

(FILE 'HOME' ENTERED AT 13:30:58 ON 06 JUN 2003)

FILE 'USPATFULL, CAPLUS' ENTERED AT 13:31:19 ON 06 JUN 2003

L1	1547	FILE	USPATFULL	
L2	7069	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L3	8616	S	COX-2 OR COX2 OR CYCLOOXYGENASE-2 OR CYCLOOXYGENASE2 OR CYCLO	
L4	454	FILE	USPATFULL	
L5	573	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L6	1027	S	162011-90-7/RN OR 162011-90-7 OR ROFECOXIB OR VIOXX OR (MK 09	
L7	576	FILE	USPATFULL	
L8	745	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L9	1321	S	CELECOXIB OR CELEBREX OR (SC58635) OR (SC58635) OR (SC-58635)	
L10	454	FILE	USPATFULL	
L11	573	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L12	1027	S	162011-90-7/RN OR 162011-90-7 OR ROFECOXIB OR VIOXX OR (MK 09	
L13	579	FILE	USPATFULL	
L14	745	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L15	1324	S	CELECOXIB OR CELEBREX OR (SC58635) OR (SC58635) OR (SC-58635)	
L16	1	FILE	USPATFULL	
L17	1	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L18	2	S	ACUTE MUCOSAL EFFECT	
L19	9	FILE	USPATFULL	
L20	53	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L21	62	S	(ACUTE (4A) MUCOSAL (4A) EFFECT?)	
L22	57401	FILE	USPATFULL	
L23	74424	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L24	131825	S	FATIGUE	
L25	7764	FILE	USPATFULL	
L26	13345	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L27	21109	S	DIARRHEA	
L28	7811	FILE	USPATFULL	
L29	13412	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L30	21223	S	DIARRHEA OR (LOOSE STOOL)	
L31	163	FILE	USPATFULL	
L32	53	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L33	216	S	(RECTAL BLEEDING)	
L34	715	FILE	USPATFULL	
L35	95	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L36	810	S	PROCTITIS	
L37	774	FILE	USPATFULL	
L38	198	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L39	972	S	PROCTITIS OR (INFLAMMATION (3A) (RECTUM OR RECTAL))	
L40	786	FILE	USPATFULL	
L41	202	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L42	988	S	PROCTITIS OR (INFLAMMATION (3A) (RECTUM OR RECTAL OR ANUS OR	
L43	12	FILE	USPATFULL	
L44	3	FILE	CAPLUS	
TOTAL FOR ALL FILES				
L45	15	S	SIGMOIDITIS OR (INHLAMMATION (4A) SIGMOID? (4A) COLON)	

L46 12 FILE USPATFULL  
 L47 3 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L48 15 S SIGMOIDITIS OR (INHLAMMATION (4A) SIGMOID? (4A) (INTERSTINE O  
 L49 16 FILE USPATFULL  
 L50 3 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L51 19 S SIGMOIDITIS OR (INFLAMMATION (4A) SIGMOID? (4A) (INTERSTINE O  
 L52 16 FILE USPATFULL  
 L53 3 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L54 19 S SIGMOIDITIS OR (INFLAMMATION (4A) SIGMOID? (4A) (INTESTINE OR  
 L55 1023 FILE USPATFULL  
 L56 600 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L57 1623 S PROSTATITIS OR (INFLAMMATION (5A) PROSTATE)  
 L58 1569 FILE USPATFULL  
 L59 1108 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L60 2677 S CYSTITIS OR (INFLAMMATION (5A) BLADDER)  
 L61 11019 FILE USPATFULL  
 L62 13518 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L63 24537 S DERMATITIS OR (INFLAMMATION (5A) SKIN)  
 L64 437 FILE USPATFULL  
 L65 426 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L66 863 S (URINARY (3A) FREQUEN?)  
 L67 2 FILE USPATFULL  
 L68 5 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L69 7 S L21 (1S) TREAT?  
 L70 5238 FILE USPATFULL  
 L71 8341 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L72 13579 S L24 (1S) TREAT?  
 L73 3578 FILE USPATFULL  
 L74 3160 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L75 6738 S L30 (1S) TREAT?  
 L76 79 FILE USPATFULL  
 L77 18 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L78 97 S L33 (1S) TREAT?  
 L79 476 FILE USPATFULL  
 L80 102 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L81 578 S L42 (1S) TREAT?  
 L82 7 FILE USPATFULL  
 L83 2 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L84 9 S L51 (1S) TREAT?  
 L85 677 FILE USPATFULL  
 L86 267 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L87 944 S L57 (1S) TREAT?  
 L88 882 FILE USPATFULL  
 L89 386 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L90 1268 S L60 (1S) TREAT?  
 L91 7480 FILE USPATFULL  
 L92 3288 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L93 10768 S L63 (1S) TREAT?

L94	156	FILE	USPATFULL
L95	191	FILE	CAPLUS
TOTAL FOR ALL FILES			
L96	347	S L66 (1S)	TREAT?
L97	625	FILE	USPATFULL
L98	989	FILE	CAPLUS
TOTAL FOR ALL FILES			
L99	1614	S L12 OR L15	
L100	0	FILE	USPATFULL
L101	0	FILE	CAPLUS
TOTAL FOR ALL FILES			
L102	0	S L99 (3S)	L69
L103	3	FILE	USPATFULL
L104	1	FILE	CAPLUS
TOTAL FOR ALL FILES			
L105	4	S L99 (3S)	L72
L106	1	FILE	USPATFULL
L107	4	FILE	CAPLUS
TOTAL FOR ALL FILES			
L108	5	S L99 (3S)	L75
L109	0	FILE	USPATFULL
L110	1	FILE	CAPLUS
TOTAL FOR ALL FILES			
L111	1	S L99 (3S)	L81
L112	0	FILE	USPATFULL
L113	0	FILE	CAPLUS
TOTAL FOR ALL FILES			
L114	0	S L99 (3S)	L84
L115	1	FILE	USPATFULL
L116	2	FILE	CAPLUS
TOTAL FOR ALL FILES			
L117	3	S L99 (3S)	L87
L118	0	FILE	USPATFULL
L119	0	FILE	CAPLUS
TOTAL FOR ALL FILES			
L120	0	S L99 (3S)	L90
L121	0	FILE	USPATFULL
L122	8	FILE	CAPLUS
TOTAL FOR ALL FILES			
L123	8	S L99 (3S)	L93
L124	0	FILE	USPATFULL
L125	0	FILE	CAPLUS
TOTAL FOR ALL FILES			
L126	0	S L99 (3S)	L96
L127	625	FILE	USPATFULL
L128	5	FILE	USPATFULL
L129	9	FILE	USPATFULL
L130	25	FILE	CAPLUS
TOTAL FOR ALL FILES			
L131	34	S L21 AND	TREAT?
L132	19027	FILE	USPATFULL
L133	11676	FILE	CAPLUS
TOTAL FOR ALL FILES			
L134	30703	S L24 AND	TREAT?
L135	7445	FILE	USPATFULL
L136	5127	FILE	CAPLUS
TOTAL FOR ALL FILES			
L137	12572	S L30 AND	TREAT?
L138	160	FILE	USPATFULL
L139	30	FILE	CAPLUS
TOTAL FOR ALL FILES			
L140	190	S L33 AND	TREAT?
L141	779	FILE	USPATFULL
L142	134	FILE	CAPLUS

TOTAL FOR ALL FILES	
L143	913 S L42 AND TREAT?
L144	16 FILE USPATFULL
L145	3 FILE CAPLUS
TOTAL FOR ALL FILES	
L146	19 S L51 AND TREAT?
L147	997 FILE USPATFULL
L148	330 FILE CAPLUS
TOTAL FOR ALL FILES	
L149	1327 S L57 AND TREAT?
L150	1524 FILE USPATFULL
L151	558 FILE CAPLUS
TOTAL FOR ALL FILES	
L152	2082 S L60 AND TREAT?
L153	10661 FILE USPATFULL
L154	5030 FILE CAPLUS
TOTAL FOR ALL FILES	
L155	15691 S L63 AND TREAT?
L156	414 FILE USPATFULL
L157	258 FILE CAPLUS
TOTAL FOR ALL FILES	
L158	672 S L66 AND TREAT?
L159	1 FILE USPATFULL
L160	1 FILE CAPLUS
TOTAL FOR ALL FILES	
L161	2 S L131 AND L99
L162	58 FILE USPATFULL
L163	2 FILE CAPLUS
TOTAL FOR ALL FILES	
L164	60 S L134 AND L99
L165	68 FILE USPATFULL
L166	10 FILE CAPLUS
TOTAL FOR ALL FILES	
L167	78 S L137 AND L99
L168	8 FILE USPATFULL
L169	0 FILE CAPLUS
TOTAL FOR ALL FILES	
L170	8 S L140 AND L99
L171	5 FILE USPATFULL
L172	2 FILE CAPLUS
TOTAL FOR ALL FILES	
L173	7 S L143 AND L99
L174	1 FILE USPATFULL
L175	1 FILE CAPLUS
TOTAL FOR ALL FILES	
L176	2 S L146 AND L99
L177	15 FILE USPATFULL
L178	3 FILE CAPLUS
TOTAL FOR ALL FILES	
L179	18 S L149 AND L99
L180	17 FILE USPATFULL
L181	1 FILE CAPLUS
TOTAL FOR ALL FILES	
L182	18 S L152 AND L99
L183	174 FILE USPATFULL
L184	16 FILE CAPLUS
TOTAL FOR ALL FILES	
L185	190 S L155 AND L99
L186	4 FILE USPATFULL
L187	0 FILE CAPLUS
TOTAL FOR ALL FILES	
L188	4 S L158 AND L99
L189	241 FILE USPATFULL
L190	29 FILE CAPLUS

TOTAL FOR ALL FILES

L191 270 S L159-L188  
L192 75708 FILE USPATFULL  
L193 103192 FILE CAPLUS

TOTAL FOR ALL FILES

L194 178900 S L21 OR L24 OR L30 OR L33 OR L42 OR L51 OR L57 OR L60 OR L63 O  
L195 8 FILE USPATFULL  
L196 35 FILE CAPLUS

TOTAL FOR ALL FILES

L197 43 S L194 (2S) L99  
L198 7 FILE USPATFULL  
L199 29 FILE CAPLUS

TOTAL FOR ALL FILES

L200 36 S L197 AND L191

FILE 'USPATFULL, CAPLUS' ENTERED AT 13:31:19 ON 06 JUN 2003

L1	1547	FILE USPATFULL
L2	7069	FILE CAPLUS
TOTAL FOR ALL FILES		
L3	8616	S COX-2 OR COX2 OR CYCLOOXYGENASE-2 OR CYCLOOXYGENASE2 OR CYCLO
L4	454	FILE USPATFULL
L5	573	FILE CAPLUS
TOTAL FOR ALL FILES		
L6	1027	S 162011-90-7/RN OR 162011-90-7 OR ROFECOXIB OR VIOXX OR (MK 09
L7	576	FILE USPATFULL
L8	745	FILE CAPLUS
TOTAL FOR ALL FILES		
L9	1321	S CELECOXIB OR CELEBREX OR (SC58635) OR (SC58635) OR (SC-58635)
L10	454	FILE USPATFULL
L11	573	FILE CAPLUS
TOTAL FOR ALL FILES		
L12	1027	S 162011-90-7/RN OR 162011-90-7 OR ROFECOXIB OR VIOXX OR (MK 09
L13	579	FILE USPATFULL
L14	745	FILE CAPLUS
TOTAL FOR ALL FILES		
L15	1324	S CELECOXIB OR CELEBREX OR (SC58635) OR (SC58635) OR (SC-58635)
L16	1	FILE USPATFULL
L17	1	FILE CAPLUS
TOTAL FOR ALL FILES		
L18	2	S ACUTE MUCOSAL EFFECT
L19	9	FILE USPATFULL
L20	53	FILE CAPLUS
TOTAL FOR ALL FILES		
L21	62	S (ACUTE (4A) MUCOSAL (4A) EFFECT?)
L22	57401	FILE USPATFULL
L23	74424	FILE CAPLUS
TOTAL FOR ALL FILES		
L24	131825	S FATIGUE
L25	7764	FILE USPATFULL
L26	13345	FILE CAPLUS
TOTAL FOR ALL FILES		
L27	21109	S DIARRHEA
L28	7811	FILE USPATFULL
L29	13412	FILE CAPLUS
TOTAL FOR ALL FILES		
L30	21223	S DIARRHEA OR (LOOSE STOOL)
L31	163	FILE USPATFULL
L32	53	FILE CAPLUS
TOTAL FOR ALL FILES		
L33	216	S (RECTAL BLEEDING)
L34	715	FILE USPATFULL
L35	95	FILE CAPLUS
TOTAL FOR ALL FILES		
L36	810	S PROCTITIS
L37	774	FILE USPATFULL
L38	198	FILE CAPLUS
TOTAL FOR ALL FILES		
L39	972	S PROCTITIS OR (INFLAMMATION (3A) (RECTUM OR RECTAL))
L40	786	FILE USPATFULL
L41	202	FILE CAPLUS
TOTAL FOR ALL FILES		
L42	988	S PROCTITIS OR (INFLAMMATION (3A) (RECTUM OR RECTAL OR ANUS OR
L43	12	FILE USPATFULL
L44	3	FILE CAPLUS
TOTAL FOR ALL FILES		
L45	15	S SIGMOIDITIS OR (INHLAMMATION (4A) SIGMOID? (4A) COLON)
L46	12	FILE USPATFULL
L47	3	FILE CAPLUS

TOTAL FOR ALL FILES  
 L48 15 S SIGMOIDITIS OR (INHLAMMATION (4A) SIGMOID? (4A) (INTERSTINE O  
 L49 16 FILE USPATFULL  
 L50 3 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L51 19 S SIGMOIDITIS OR (INFLAMMATION (4A) SIGMOID? (4A) (INTERSTINE O  
 L52 16 FILE USPATFULL  
 L53 3 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L54 19 S SIGMOIDITIS OR (INFLAMMATION (4A) SIGMOID? (4A) (INTESTINE OR  
 L55 1023 FILE USPATFULL  
 L56 600 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L57 1623 S PROSTATITIS OR (INFLAMMATION (5A) PROSTATE)  
 L58 1569 FILE USPATFULL  
 L59 1108 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L60 2677 S CYSTITIS OR (INFLAMMATION (5A) BLADDER)  
 L61 11019 FILE USPATFULL  
 L62 13518 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L63 24537 S DERMATITIS OR (INFLAMMATION (5A) SKIN)  
 L64 437 FILE USPATFULL  
 L65 426 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L66 863 S (URINARY (3A) FREQUEN?)  
 L67 2 FILE USPATFULL  
 L68 5 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L69 7 S L21 (1S) TREAT?  
 L70 5238 FILE USPATFULL  
 L71 8341 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L72 13579 S L24 (1S) TREAT?  
 L73 3578 FILE USPATFULL  
 L74 3160 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L75 6738 S L30 (1S) TREAT?  
 L76 79 FILE USPATFULL  
 L77 18 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L78 97 S L33 (1S) TREAT?  
 L79 476 FILE USPATFULL  
 L80 102 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L81 578 S L42 (1S) TREAT?  
 L82 7 FILE USPATFULL  
 L83 2 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L84 9 S L51 (1S) TREAT?  
 L85 677 FILE USPATFULL  
 L86 267 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L87 944 S L57 (1S) TREAT?  
 L88 882 FILE USPATFULL  
 L89 386 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L90 1268 S L60 (1S) TREAT?  
 L91 7480 FILE USPATFULL  
 L92 3288 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L93 10768 S L63 (1S) TREAT?  
 L94 156 FILE USPATFULL  
 L95 191 FILE CAPLUS

TOTAL FOR ALL FILES  
 L96 347 S L66 (1S) TREAT?  
 L97 625 FILE USPATFULL  
 L98 989 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L99 1614 S L12 OR L15  
 L100 0 FILE USPATFULL  
 L101 0 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L102 0 S L99 (3S) L69  
 L103 3 FILE USPATFULL  
 L104 1 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L105 4 S L99 (3S) L72  
 L106 1 FILE USPATFULL  
 L107 4 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L108 5 S L99 (3S) L75  
 L109 0 FILE USPATFULL  
 L110 1 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L111 1 S L99 (3S) L81  
 L112 0 FILE USPATFULL  
 L113 0 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L114 0 S L99 (3S) L84  
 L115 1 FILE USPATFULL  
 L116 2 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L117 3 S L99 (3S) L87  
 L118 0 FILE USPATFULL  
 L119 0 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L120 0 S L99 (3S) L90  
 L121 0 FILE USPATFULL  
 L122 8 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L123 8 S L99 (3S) L93  
 L124 0 FILE USPATFULL  
 L125 0 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L126 0 S L99 (3S) L96  
 L127 625 FILE USPATFULL  
 L128 5 FILE USPATFULL  
 L129 9 FILE USPATFULL  
 L130 25 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L131 34 S L21 AND TREAT?  
 L132 19027 FILE USPATFULL  
 L133 11676 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L134 30703 S L24 AND TREAT?  
 L135 7445 FILE USPATFULL  
 L136 5127 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L137 12572 S L30 AND TREAT?  
 L138 160 FILE USPATFULL  
 L139 30 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L140 190 S L33 AND TREAT?  
 L141 779 FILE USPATFULL  
 L142 134 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L143 913 S L42 AND TREAT?

L144	16	FILE	USPATFULL
L145	3	FILE	CAPLUS
TOTAL FOR ALL FILES			
L146	19	S	L51 AND TREAT?
L147	997	FILE	USPATFULL
L148	330	FILE	CAPLUS
TOTAL FOR ALL FILES			
L149	1327	S	L57 AND TREAT?
L150	1524	FILE	USPATFULL
L151	558	FILE	CAPLUS
TOTAL FOR ALL FILES			
L152	2082	S	L60 AND TREAT?
L153	10661	FILE	USPATFULL
L154	5030	FILE	CAPLUS
TOTAL FOR ALL FILES			
L155	15691	S	L63 AND TREAT?
L156	414	FILE	USPATFULL
L157	258	FILE	CAPLUS
TOTAL FOR ALL FILES			
L158	672	S	L66 AND TREAT?
L159	1	FILE	USPATFULL
L160	1	FILE	CAPLUS
TOTAL FOR ALL FILES			
L161	2	S	L131 AND L99
L162	58	FILE	USPATFULL
L163	2	FILE	CAPLUS
TOTAL FOR ALL FILES			
L164	60	S	L134 AND L99
L165	68	FILE	USPATFULL
L166	10	FILE	CAPLUS
TOTAL FOR ALL FILES			
L167	78	S	L137 AND L99
L168	8	FILE	USPATFULL
L169	0	FILE	CAPLUS
TOTAL FOR ALL FILES			
L170	8	S	L140 AND L99
L171	5	FILE	USPATFULL
L172	2	FILE	CAPLUS
TOTAL FOR ALL FILES			
L173	7	S	L143 AND L99
L174	1	FILE	USPATFULL
L175	1	FILE	CAPLUS
TOTAL FOR ALL FILES			
L176	2	S	L146 AND L99
L177	15	FILE	USPATFULL
L178	3	FILE	CAPLUS
TOTAL FOR ALL FILES			
L179	18	S	L149 AND L99
L180	17	FILE	USPATFULL
L181	1	FILE	CAPLUS
TOTAL FOR ALL FILES			
L182	18	S	L152 AND L99
L183	174	FILE	USPATFULL
L184	16	FILE	CAPLUS
TOTAL FOR ALL FILES			
L185	190	S	L155 AND L99
L186	4	FILE	USPATFULL
L187	0	FILE	CAPLUS
TOTAL FOR ALL FILES			
L188	4	S	L158 AND L99
L189	241	FILE	USPATFULL
L190	29	FILE	CAPLUS
TOTAL FOR ALL FILES			
L191	270	S	L159-L188

```

L192      75708 FILE USPATFULL
L193      103192 FILE CAPLUS
TOTAL FOR ALL FILES
L194      178900 S L21 OR L24 OR L30 OR L33 OR L42 OR L51 OR L57 OR L60 OR L63 O
L195      8 FILE USPATFULL
L196      35 FILE CAPLUS
TOTAL FOR ALL FILES
L197      43 S L194 (2S) L99
L198      7 FILE USPATFULL
L199      29 FILE CAPLUS
TOTAL FOR ALL FILES
L200      36 S L197 AND L191

```

=> sace all

SACE IS NOT A RECOGNIZED COMMAND

The previous command name entered was not recognized by the system.

For a list of commands available to you in the current file, enter

"HELP COMMANDS" at an arrow prompt (=>).

=> save all

ENTER NAME OR (END):cox2rad/l

L# LIST L1-L200 HAS BEEN SAVED AS 'COX2RAD/L'

=> save all  
ENTER NAME OR (END):cox2rad/l  
L# LIST L1-L200 HAS BEEN SAVED AS 'COX2RAD/L'  
  
=> d his

(FILE 'HOME' ENTERED AT 13:30:58 ON 06 JUN 2003)

FILE 'USPATFULL, CAPLUS' ENTERED AT 13:31:19 ON 06 JUN 2003

L1	1547	FILE	USPATFULL	
L2	7069	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L3	8616	S	COX-2 OR COX2 OR CYCLOOXYGENASE-2 OR CYCLOOXYGENASE2 OR CYCLO	
L4	454	FILE	USPATFULL	
L5	573	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L6	1027	S	162011-90-7/RN OR 162011-90-7 OR ROFECOXIB OR VIOXX OR (MK 09	
L7	576	FILE	USPATFULL	
L8	745	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L9	1321	S	CELECOXIB OR CELEBREX OR (SC58635) OR (SC58635) OR (SC-58635)	
L10	454	FILE	USPATFULL	
L11	573	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L12	1027	S	162011-90-7/RN OR 162011-90-7 OR ROFECOXIB OR VIOXX OR (MK 09	
L13	579	FILE	USPATFULL	
L14	745	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L15	1324	S	CELECOXIB OR CELEBREX OR (SC58635) OR (SC58635) OR (SC-58635)	
L16	1	FILE	USPATFULL	
L17	1	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L18	2	S	ACUTE MUCOSAL EFFECT	
L19	9	FILE	USPATFULL	
L20	53	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L21	62	S	(ACUTE (4A) MUCOSAL (4A) EFFECT?)	
L22	57401	FILE	USPATFULL	
L23	74424	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L24	131825	S	FATIGUE	
L25	7764	FILE	USPATFULL	
L26	13345	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L27	21109	S	DIARRHEA	
L28	7811	FILE	USPATFULL	
L29	13412	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L30	21223	S	DIARRHEA OR (LOOSE STOOL)	
L31	163	FILE	USPATFULL	
L32	53	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L33	216	S	(RECTAL BLEEDING)	
L34	715	FILE	USPATFULL	
L35	95	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L36	810	S	PROCTITIS	
L37	774	FILE	USPATFULL	
L38	198	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	
L39	972	S	PROCTITIS OR (INFLAMMATION (3A) (RECTUM OR RECTAL))	
L40	786	FILE	USPATFULL	
L41	202	FILE	CAPLUS	
		TOTAL	FOR ALL FILES	

L42 988 S PROCTITIS OR (INFLAMMATION (3A) (RECTUM OR RECTAL OR ANUS OR  
 L43 12 FILE USPATFULL  
 L44 3 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L45 15 S SIGMOIDITIS OR (INHLAMMATION (4A) SIGMOID? (4A) COLON)  
 L46 12 FILE USPATFULL  
 L47 3 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L48 15 S SIGMOIDITIS OR (INHLAMMATION (4A) SIGMOID? (4A) (INTERSTINE O  
 L49 16 FILE USPATFULL  
 L50 3 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L51 19 S SIGMOIDITIS OR (INFLAMMATION (4A) SIGMOID? (4A) (INTERSTINE O  
 L52 16 FILE USPATFULL  
 L53 3 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L54 19 S SIGMOIDITIS OR (INFLAMMATION (4A) SIGMOID? (4A) (INTESTINE OR  
 L55 1023 FILE USPATFULL  
 L56 600 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L57 1623 S PROSTATITIS OR (INFLAMMATION (5A) PROSTATE)  
 L58 1569 FILE USPATFULL  
 L59 1108 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L60 2677 S CYSTITIS OR (INFLAMMATION (5A) BLADDER)  
 L61 11019 FILE USPATFULL  
 L62 13518 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L63 24537 S DERMATITIS OR (INFLAMMATION (5A) SKIN)  
 L64 437 FILE USPATFULL  
 L65 426 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L66 863 S (URINARY (3A) FREQUEN?)  
 L67 2 FILE USPATFULL  
 L68 5 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L69 7 S L21 (1S) TREAT?  
 L70 5238 FILE USPATFULL  
 L71 8341 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L72 13579 S L24 (1S) TREAT?  
 L73 3578 FILE USPATFULL  
 L74 3160 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L75 6738 S L30 (1S) TREAT?  
 L76 79 FILE USPATFULL  
 L77 18 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L78 97 S L33 (1S) TREAT?  
 L79 476 FILE USPATFULL  
 L80 102 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L81 578 S L42 (1S) TREAT?  
 L82 7 FILE USPATFULL  
 L83 2 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L84 9 S L51 (1S) TREAT?  
 L85 677 FILE USPATFULL  
 L86 267 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L87 944 S L57 (1S) TREAT?  
 L88 882 FILE USPATFULL  
 L89 386 FILE CAPLUS  
 TOTAL FOR ALL FILES

L90	1268 S L60 (1S) TREAT?
L91	7480 FILE USPATFULL
L92	3288 FILE CAPLUS
TOTAL FOR ALL FILES	
L93	10768 S L63 (1S) TREAT?
L94	156 FILE USPATFULL
L95	191 FILE CAPLUS
TOTAL FOR ALL FILES	
L96	347 S L66 (1S) TREAT?
L97	625 FILE USPATFULL
L98	989 FILE CAPLUS
TOTAL FOR ALL FILES	
L99	1614 S L12 OR L15
L100	0 FILE USPATFULL
L101	0 FILE CAPLUS
TOTAL FOR ALL FILES	
L102	0 S L99 (3S) L69
L103	3 FILE USPATFULL
L104	1 FILE CAPLUS
TOTAL FOR ALL FILES	
L105	4 S L99 (3S) L72
L106	1 FILE USPATFULL
L107	4 FILE CAPLUS
TOTAL FOR ALL FILES	
L108	5 S L99 (3S) L75
L109	0 FILE USPATFULL
L110	1 FILE CAPLUS
TOTAL FOR ALL FILES	
L111	1 S L99 (3S) L81
L112	0 FILE USPATFULL
L113	0 FILE CAPLUS
TOTAL FOR ALL FILES	
L114	0 S L99 (3S) L84
L115	1 FILE USPATFULL
L116	2 FILE CAPLUS
TOTAL FOR ALL FILES	
L117	3 S L99 (3S) L87
L118	0 FILE USPATFULL
L119	0 FILE CAPLUS
TOTAL FOR ALL FILES	
L120	0 S L99 (3S) L90
L121	0 FILE USPATFULL
L122	8 FILE CAPLUS
TOTAL FOR ALL FILES	
L123	8 S L99 (3S) L93
L124	0 FILE USPATFULL
L125	0 FILE CAPLUS
TOTAL FOR ALL FILES	
L126	0 S L99 (3S) L96
L127	625 FILE USPATFULL
L128	5 FILE USPATFULL
L129	9 FILE USPATFULL
L130	25 FILE CAPLUS
TOTAL FOR ALL FILES	
L131	34 S L21 AND TREAT?
L132	19027 FILE USPATFULL
L133	11676 FILE CAPLUS
TOTAL FOR ALL FILES	
L134	30703 S L24 AND TREAT?
L135	7445 FILE USPATFULL
L136	5127 FILE CAPLUS
TOTAL FOR ALL FILES	
L137	12572 S L30 AND TREAT?
L138	160 FILE USPATFULL

L139 30 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L140 190 S L33 AND TREAT?  
 L141 779 FILE USPATFULL  
 L142 134 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L143 913 S L42 AND TREAT?  
 L144 16 FILE USPATFULL  
 L145 3 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L146 19 S L51 AND TREAT?  
 L147 997 FILE USPATFULL  
 L148 330 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L149 1327 S L57 AND TREAT?  
 L150 1524 FILE USPATFULL  
 L151 558 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L152 2082 S L60 AND TREAT?  
 L153 10661 FILE USPATFULL  
 L154 5030 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L155 15691 S L63 AND TREAT?  
 L156 414 FILE USPATFULL  
 L157 258 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L158 672 S L66 AND TREAT?  
 L159 1 FILE USPATFULL  
 L160 1 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L161 2 S L131 AND L99  
 L162 58 FILE USPATFULL  
 L163 2 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L164 60 S L134 AND L99  
 L165 68 FILE USPATFULL  
 L166 10 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L167 78 S L137 AND L99  
 L168 8 FILE USPATFULL  
 L169 0 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L170 8 S L140 AND L99  
 L171 5 FILE USPATFULL  
 L172 2 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L173 7 S L143 AND L99  
 L174 1 FILE USPATFULL  
 L175 1 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L176 2 S L146 AND L99  
 L177 15 FILE USPATFULL  
 L178 3 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L179 18 S L149 AND L99  
 L180 17 FILE USPATFULL  
 L181 1 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L182 18 S L152 AND L99  
 L183 174 FILE USPATFULL  
 L184 16 FILE CAPLUS  
 TOTAL FOR ALL FILES  
 L185 190 S L155 AND L99  
 L186 4 FILE USPATFULL

L187           0 FILE CAPLUS  
TOTAL FOR ALL FILES  
L188           4 S L158 AND L99  
L189           241 FILE USPATFULL  
L190           29 FILE CAPLUS  
TOTAL FOR ALL FILES  
L191           270 S L159-L188  
L192           75708 FILE USPATFULL  
L193           103192 FILE CAPLUS  
TOTAL FOR ALL FILES  
L194           178900 S L21 OR L24 OR L30 OR L33 OR L42 OR L51 OR L57 OR L60 OR L63 O  
L195           8 FILE USPATFULL  
L196           35 FILE CAPLUS  
TOTAL FOR ALL FILES  
L197           43 S L194 (2S) L99  
L198           7 FILE USPATFULL  
L199           29 FILE CAPLUS  
TOTAL FOR ALL FILES  
L200           36 S L197 AND L191  
              SAVE ALL COX2RAD/L

L200 ANSWER 28 OF 36 CAPLUS COPYRIGHT 2003 ACS

AN 2001:904209 CAPLUS

DN 136:31724

TI Heterocycle derivatives and methods of use

IN Peterson, Johnny W.; Gessell-Lee, Deborah L.; Saini, Shamsher S.

PA The University of Texas System, USA

SO PCT Int. Appl., 88 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07H019-20

CC 1-12 (Pharmacology)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001094369	A2	20011213	WO 2001-US16190	20010519
	W:				
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				
	CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,				
	HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,				
	LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,				
	RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,				
	VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,				
	DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,				
	BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2002032228	A1	20020314	US 2001-860652	20010519
	US 20020188016	A9	20021212		
PRAI	US 2000-210412P	P	20000608		
OS	MARPAT 136:31724				
AB	The present invention provides methods for <b>treating</b> intestinal fluid loss, whooping cough, anthrax, and conditions assocd. with smooth muscle contraction. The present invention also provides methods for inhibiting adenylate cyclase in vivo and in vitro.				
ST	heterocycle deriv adenylate cyclase inhibition <b>diarrhea</b> ; intestinal fluid loss <b>treatment</b> heterocycle deriv; smooth muscle contraction inhibition heterocycle deriv; whooping cough <b>treatment</b> heterocycle deriv				
IT	Animal cell (adenylate cyclase-contg.; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for <b>treating</b> intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)				
IT	Prostaglandins RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (analogs; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for <b>treating</b> intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)				
IT	Bacillus anthracis (anthrax from; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for <b>treating</b> intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)				
IT	Heterocyclic compounds RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (arom., di-Ph; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for <b>treating</b> intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)				
IT	ADP ribosylation (by pathogenic organisms; heterocycle derivs. for inhibiting adenylate				

cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Toxins

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (cholera, intestinal fluid loss stimulation by; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Intestine, disease

(fluid loss; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Antidiarrheals

Pertussis

(heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Heterocyclic compounds

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Aromatic compounds

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (heterocyclic, di-Ph; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Intestine, disease

(infection, fluid loss assocd. with pathogenic; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Pathogen

(intestinal fluid loss assocd. with; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Body fluid

(loss; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Muscle relaxants

(smooth; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT 56-65-5, 5'-ATP, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study) (cAMP formation from; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT 363-24-6, PGE2

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(cAMP formation stimulation by and reaction with L-histidine; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax)

IT 60-92-4, CAMP  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (formation; heterocycle derivs. for inhibiting adenylate cyclase and  
 methods of use for **treating** intestinal fluid loss and  
 whooping cough and anthrax and conditions assocd. with smooth muscle  
 contraction)

IT 9012-42-4, Adenylate cyclase  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (heterocycle derivs. for inhibiting adenylate cyclase and methods of  
 use for **treating** intestinal fluid loss and whooping cough and  
 anthrax and conditions assocd. with smooth muscle contraction)

IT 380153-74-2 380153-75-3  
 RL: DMA (Drug mechanism of action); FMU (Formation, unclassified); PAC  
 (Pharmacological activity); THU (Therapeutic use); BIOL (Biological  
 study); FORM (Formation, nonpreparative); USES (Uses)  
 (heterocycle derivs. for inhibiting adenylate cyclase and methods of  
 use for **treating** intestinal fluid loss and whooping cough and  
 anthrax and conditions assocd. with smooth muscle contraction)

IT 53-86-1, Indomethacin 71-00-1, L-Histidine, biological studies  
 288-32-4, Imidazole, biological studies 443-48-1, Metronidazole  
 88149-94-4 162011-90-7 169590-42-5 188817-13-2  
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU  
 (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (heterocycle derivs. for inhibiting adenylate cyclase and methods of  
 use for **treating** intestinal fluid loss and whooping cough and  
 anthrax and conditions assocd. with smooth muscle contraction)

L200 ANSWER 29 OF 36 CAPLUS COPYRIGHT 2003 ACS  
 AN 2001:857055 CAPLUS  
 DN 136:194000  
 TI **Celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the  
 severity of experimental colitis induced by dinitrobenzene sulfonic acid  
 in rats  
 AU Cuzzocrea, Salvatore; Mazzon, Emanuela; Serraino, Ivana; Dugo, Laura;  
 Centorrino, Tommaso; Ciccolo, Antonio; Sautebin, Lidia; Caputi, Achille P.  
 CS Institute of Pharmacology, School of Medicine, University of Messina,  
 Torre Biologica, Policlinico Universitario Via C. Valera, Gazzi, Messina,  
 98100, Italy  
 SO European Journal of Pharmacology (2001), 431(1), 91-102  
 CODEN: EJPHAZ; ISSN: 0014-2999  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 CC 1-9 (Pharmacology)  
 AB Inflammatory bowel disease is characterized by oxidative and nitrosative  
 stress, leukocyte infiltration, upregulation of the expression of  
 intercellular adhesion mol. 1 (ICAM-1) and upregulation of P-selectin in  
 the colon. Here, we investigate the effects of the selective  
 cyclo-oxygenase-2 inhibitor, **celecoxib**, in rats subjected to  
 exptl. colitis. Colitis was induced in rats by intracolonic instillation  
 of dinitrobenzene sulfonic acid (DNBS). Rats experienced hemorrhagic  
**diarrhea** and wt. loss. At 4 days after administration of DNBS,  
 the mucosa of the colon exhibited large areas of necrosis. Neutrophil  
 infiltration (detd. by histol., as well as an increase in myeloperoxidase  
 activity in the mucosa) was assocd. with upregulation of ICAM-1 and  
 P-selectin, as well as high tissue levels of malondialdehyde.  
 Immunohistochem. for nitrotyrosine and poly(ADP-ribose) polymerase showed  
 intense staining in the inflamed colon. **Celecoxib** (5 mg/kg  
 twice a day orally) significantly reduced the degree of hemorrhagic  
**diarrhea** and the wt. loss caused by administration of DNBS.  
**Celecoxib** also caused a substantial redn. of (i) the degree of  
 colonic injury, (ii) the rise in myeloperoxidase activity (mucosa), (iii)  
 the increase in the tissue levels of malondialdehyde, (iv) the increase in  
 staining (immunohistochem.) for nitrotyrosine, as well as (v) the

upregulation of ICAM-1 and P-selectin caused by DNBS in the colon. Thus, we provide the first evidence that a selective cyclo-oxygenase-2 inhibitor **celecoxib** reduces the degree of colitis caused by DNBS.

ST **celecoxib colitis treatment**

IT Cell adhesion molecules

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(ICAM-1 (intercellular adhesion mol. 1); **celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT Selectins

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(P-; **celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT Oxidative stress, biological

(**celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT Intestine, disease

(colitis; **celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT Neutrophil

(infiltration; **celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT Stress, animal

(nitrosative; **celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT 9003-99-0, Myeloperoxidase

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(**celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT 169590-42-5, Celecoxib

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(**celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

RE.CNT 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Ajuebor, M; Am J Physiol: Gastrointest Liver Physiol 2000, V279, PG238  
CAPLUS

(2) Allgayer, H; Gastroenterology 1989, V96, P1290 CAPLUS

(3) Andborn, W; Inflammatory Bowel Dis 1999, V2, P119

(4) Bjarnson, I; Gastroenterology 1993, V104, P1832

(5) Bradford, M; Anal Biochem 1976, V72, P248 CAPLUS

(6) Carty, E; Gut 2000, V46, P487 CAPLUS

(7) Challa, A; Carcinogenesis 1997, V18, P2023 CAPLUS

(8) Chan, C; J Pharmacol Exp Ther 1995, V274, P1531 CAPLUS

(9) Chanvitayapongs, S; NeuroReport 1997, V8, P1499 CAPLUS

(10) Cohn, S; J Clin Invest 1997, V99, P1327

(11) Cuzzocrea, S; J Immunol 1999, V22, P5094

(12) Dreiser, R; Drugs 1993, V46, P270

(13) Duthie, S; Eur J Nutr 1999, V38, P28 CAPLUS

(14) D'Haens, G; Gastroenterology 1999, V116, P1029 CAPLUS

(15) Eiserich, J; Nature 1998, V391, P393 CAPLUS

(16) Fedorak, R; Gastroenterology 1990, V98, P615 CAPLUS

(17) Fries, W; Lab Invest 1999, V79, P49 MEDLINE

(18) Fukuda, K; J Ethnopharmacol 1999, V66, P227 CAPLUS

(19) Gibson, G; Arch Intern Med 1992, V152, P625 MEDLINE

(20) Goldstein, J; Am J Gastroenterol 2000, V95, P1681 CAPLUS

(21) Grisham, M; Lancet 1994, V344, P859 MEDLINE  
 (22) Halliwell, B; FEBS Lett 1997, V411, P157 CAPLUS  
 (23) Hoult, J; Br J Pharmacol 1978, V64, P6 CAPLUS  
 (24) Jozeau, J; Drugs 1997, V53, P563  
 (25) Karmeli, F; Eur J Gastroenterol Hepatol 2000, V12, P223 CAPLUS  
 (26) Kaufmann, H; Ann Intern Med 1987, V107, P513 MEDLINE  
 (27) Knudsen, P; J Immunol 1986, V137, P3189 CAPLUS  
 (28) Lesch, C; Methods Find Exp Clin Pharmacol 1999, V21, P99 CAPLUS  
 (29) Marcinkiewicz, J; Cytokine 1991, V3, P327 CAPLUS  
 (30) Marini, U; Drugs 1993, V46, P249  
 (31) Masferrer, J; Gastroenterol Clin North Am 1996, V25, P363 MEDLINE  
 (32) McKenzie, S; J Clin Invest 1996, V98, P136 CAPLUS  
 (33) Mizuno, H; Gastroenterology 1997, V112, P645  
 (34) Moreland, L; J Rheumatol 1996, V23, P1849 CAPLUS  
 (35) Mullane, K; J Pharmacol Methods 1985, V14, P157 CAPLUS  
 (36) Narisawa, T; Jpn J Cancer Res 1993, V84, P1007 CAPLUS  
 (37) Negoro, K; Gastroenterology 1999, V117, P1062 CAPLUS  
 (38) Ohkawa, H; Anal Biochem 1979, V95, P351 CAPLUS  
 (39) O'Banion, M; J Biol Chem 1991, V266, P23261 CAPLUS  
 (40) Present, D; N Engl J Med 1999, V340, P1398 CAPLUS  
 (41) Rachmilewitz, D; Gastroenterology 1989, V97, P326 CAPLUS  
 (42) Reuter, B; J Clin Invest 1996, V98, P483  
 (43) Ricart, E; Gastroenterology 1999, V117, P429 MEDLINE  
 (44) Seibert, K; Proc Natl Acad Sci USA 1994, V91, P12013 CAPLUS  
 (45) Sharon, P; Gastroenterology 1978, V75, P638 CAPLUS  
 (46) Shiratori, Y; Digestion 1989, V44, P163 MEDLINE  
 (47) Simmonds, N; Gastroenterology 1992, V1, P186  
 (48) Szabo, C; J Exp Med 1997, V186, P1041 CAPLUS  
 (49) Szabo, C; Trends Pharmacol Sci 1998, V19, P287 CAPLUS  
 (50) Targan, S; N Engl J Med 1997, V337, P1029 CAPLUS  
 (51) Tessner, T; Gastroenterology 1998, V115, P874 CAPLUS  
 (52) Tsujii, M; Proc Natl Acad Sci USA 1997, V94, P3336 CAPLUS  
 (53) Urthy, S; Aliment Pharmacol Ther 1999, V13, P251  
 (54) Wallace, J; Gastroenterology 1992, V102, P18 CAPLUS  
 (55) Wallace, J; Gastroenterology 1998, V115, P101 CAPLUS  
 (56) Whittle, B; Scand J Gastroenterol, Suppl 1986, V125, P128 MEDLINE  
 (57) Xie, W; Drug Dev Res 1992, V25, P249 CAPLUS  
 (58) Yamada, T; Inflammation 1993, V17, P641 CAPLUS  
 (59) Zhang, F; Carcinogenesis 1999, V20, P445 CAPLUS  
 (60) Zingarelli, B; Gastroenterology 1999, V116, P335 CAPLUS

L200 ANSWER 30 OF 36 CAPLUS COPYRIGHT 2003 ACS

AN 2001:167798 CAPLUS

DN 134:202695

TI Method for **treating** or preventing chronic **prostatitis**  
 or chronic pelvic pain syndrome with COX-2 selective inhibitor

IN Nickel, Curtis J.; Stoner, Elizabeth; Waldstreicher, Joanne; Pontari,  
 Michel A.

PA Merck & Co., Inc., USA; Temple University - of the Commonwealth System of  
 Higher Education

SO PCT Int. Appl., 13 pp.  
 CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-18

CC 1-7 (Pharmacology)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001015687	A1	20010308	WO 2000-US23100	20000824
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD,			

SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,  
 ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,  
 CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
 US 6403640 B1 20020611 US 2000-644998 20000824  
 EP 1212051 A1 20020612 EP 2000-961351 20000824  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO, MK, CY, AL  
 PRAI US 1999-151126P P 19990827  
 WO 2000-US23100 W 20000824  
 AB The use of a COX-2 selective inhibitor for the **treatment** or  
 prevention of chronic **prostatitis** or chronic pelvic pain  
 syndrome is disclosed.  
 ST COX2 inhibitor **prostatitis** chronic pelvic pain syndrome;  
 cyclooxygenase 2 inhibitor **treatment** chronic **prostatitis**  
 IT Prostate-specific antigen  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (conjugates, in combination with COX-2 inhibitor; COX-2 selective  
 inhibitor for **treatment** or prevention of chronic  
**prostatitis** or chronic pelvic pain syndrome)  
 IT Analgesics  
 Antibiotics  
 Cholinergic antagonists  
 (in combination with COX-2 inhibitor; COX-2 selective inhibitor for  
**treatment** or prevention of chronic **prostatitis** or  
 chronic pelvic pain syndrome)  
 IT Body, anatomical  
 (pelvis, chronic pelvic pain syndrome; COX-2 selective inhibitor for  
**treatment** or prevention of chronic **prostatitis** or  
 chronic pelvic pain syndrome)  
 IT Prostate gland  
 (**prostatitis**; COX-2 selective inhibitor for **treatment**  
 or prevention of chronic **prostatitis** or chronic pelvic pain  
 syndrome)  
 IT Drug delivery systems  
 (topical, urinary analgesics, in combination with COX-2 inhibitor;  
 COX-2 selective inhibitor for **treatment** or prevention of  
 chronic **prostatitis** or chronic pelvic pain syndrome)  
 IT Adrenoceptor antagonists  
 (.alpha.1-, in combination with COX-2 inhibitor; COX-2 selective  
 inhibitor for **treatment** or prevention of chronic  
**prostatitis** or chronic pelvic pain syndrome)  
 IT 51803-78-2, Nimesulide 71125-38-7, Meloxicam 80937-31-1, Flosulide  
 88149-94-4, DuP 697 123653-11-2, NS 398 **162011-90-7**,  
**Rofecoxib** 162054-19-5, SC-58125 **169590-42-5**,  
**Celecoxib** 179382-91-3, RS 57067 181695-72-7, Valdecoxib  
 198470-84-7, Parecoxib 202409-33-4, MK-663  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (COX-2 selective inhibitor for **treatment** or prevention of  
 chronic **prostatitis** or chronic pelvic pain syndrome)  
 IT 39391-18-9  
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological  
 process); BSU (Biological study, unclassified); BIOL (Biological study);  
 PROC (Process)  
 (cyclooxygenase-2, selective inhibitors; COX-2 selective inhibitor for  
**treatment** or prevention of chronic **prostatitis** or  
 chronic pelvic pain syndrome)  
 IT 9081-34-9, 5.alpha.-Reductase  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); BIOL (Biological study)  
 (inhibitors, in combination with COX-2 inhibitor; COX-2 selective  
 inhibitor for **treatment** or prevention of chronic  
**prostatitis** or chronic pelvic pain syndrome)

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Aotsuka; US 6136831 A 2000 CAPLUS
- (2) Canale; Andrologia 1993, V25(3), P163 MEDLINE
- (3) Canale; Drugs 1993, Suppl 1, P147
- (4) Grelan Pharmaceutical Co Ltd; WO 9846594 A1 1998 CAPLUS
- (5) Guess; US 6054455 A 2000 CAPLUS
- (6) Melis; Minerva Ginecologica 1997, V49(9), P409 MEDLINE
- (7) Venturini; Cephalalgia 1997, V17/20(29-30)

L200 ANSWER 31 OF 36 CAPLUS COPYRIGHT 2003 ACS

AN 2000:900773 CAPLUS

DN 134:41979

TI (Z)-Styryl acetoxypheyl sulfides as cyclooxygenase inhibitors

IN Reddy, E. Premkumar; Reddy, M. V. Ramana

PA Temple University - of the Commonwealth System of Higher Education, USA

SO PCT Int. Appl., 28 pp.

CODEN: PIXXD2

DT Patent

LA English

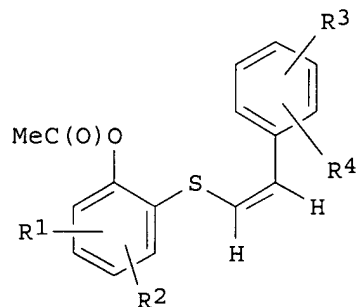
IC ICM C12N

CC 25-18 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)

Section cross-reference(s): 1, 7, 35, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000077169	A2	20001221	WO 2000-US16725	20000616
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	AU 2000056207	A5	20010102	AU 2000-56207	20000616
	EP 1191929	A2	20020403	EP 2000-941505	20000616
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
PRAI	US 1999-139445P	P	19990616		
	WO 2000-US16725	W	20000616		
OS	MARPAT 134:41979				
GI					



I

AB (Z)-Styryl acetoxypheyl sulfides (shown as I; R1, R2, R3, R4 = H, halogen, OH, C1-C8 alkyl, C1-C6 alkoxy, NO2, CN, OAc, amino, carboxy, sulfamyl, lower acylsulfamyl and trifluoromethyl), a method for their prepn., and their usefulness in **treating** inflammation and

cyclooxygenase-mediated disorders are claimed. The compds. of the invention preferably are characterized by a large selectivity ratio for cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition; data are reported for I (R1 = R2 = R3 = H; R4 = H, 4-F, 2-Cl, 4-Cl, 3-acetoxy). The claimed method of prepn. comprises reacting (Z)-styryl hydroxyphenyl sulfides with acetic anhydride. The (Z)-styryl hydroxyphenyl sulfides were made from sodium 2-hydroxybenzenethiolates and phenylacetylenes. I undergo radical polymn. to give polyolefins. (Z)-styryl acetoxypheyl sulfide was significantly more effective than Celecoxib with respect to inhibition of colorectal cancer cell colony growth.

- ST styryl acetoxypheyl sulfide prepn inhibition cyclooxygenase 2 polymn; antiinflammatory cyclooxygenase 2 inhibition styryl acetoxypheyl sulfide prepn; antitumor agent cyclooxygenase 2 inhibition styryl acetoxypheyl sulfide prepn; angiogenesis inhibitor cyclooxygenase 2 inhibition styryl acetoxypheyl sulfide prepn
- IT Bronchi  
(bronchitis; prepn. of styryl acetoxypheyl sulfides useful as inhibitors of cyclooxygenase-2 for **treating**)
- IT Digestive tract  
(disease; prepn. of styryl acetoxypheyl sulfides useful as inhibitors of cyclooxygenase-2 for **treating**)
- IT Drug delivery systems  
(of styryl acetoxypheyl sulfides useful as selective inhibitors of cyclooxygenase-2)
- IT Polyolefins  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. by radical polymn. of styryl acetoxypheyl sulfides)
- IT Antitumor agents  
(prepn. of styryl acetoxypheyl sulfides useful against neoplasias that produce prostaglandins)
- IT Burn  
**Dermatitis**  
Psoriasis  
(prepn. of styryl acetoxypheyl sulfides useful as inhibitors of cyclooxygenase-2 for **treating**)
- IT Analgesics  
Angiogenesis inhibitors  
Anti-inflammatory agents  
Antiarthritics  
Antiasthmatics  
Antipyretics  
Antiviral agents  
(prepn. of styryl acetoxypheyl sulfides useful as selective inhibitors of cyclooxygenase-2)
- IT Thioethers  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(prepn. of styryl acetoxypheyl sulfides useful as selective inhibitors of cyclooxygenase-2)
- IT Tendon  
(tendinitis; prepn. of styryl acetoxypheyl sulfides useful as inhibitors of cyclooxygenase-2 for **treating**)
- IT 536-74-3, Phenylacetylene 766-96-1, 4-Bromophenylacetylene 766-97-2,  
4-Methylphenylacetylene 766-98-3, 4-Fluorophenylacetylene 768-60-5,  
4-Methoxyphenylacetylene 873-31-4, 2-Chlorophenylacetylene 873-73-4,  
4-Chlorophenylacetylene 937-31-5, 4-Nitrophenylacetylene 10401-11-3,  
3-Hydroxyphenylacetylene 40307-11-7, 4-Ethylphenylacetylene  
79887-10-8, 4-Pentylphenylacetylene  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(addn. reactions with 2-acetoxythiophenols in presence of sodium followed by condensation with acetic anhydride)
- IT 313269-75-9, 2-Acetoxybenzenethiol  
RL: RCT (Reactant); RACT (Reactant or reagent)

(addn. reactions with phenylacetylenes in presence of sodium)

IT 1121-24-0, 2-Hydroxythiophenol  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (addn. reactions with phenylacetylenes in presence of sodium followed by condensation with acetic anhydride)

IT 39391-18-9  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (cyclooxygenase-2; prepn. of styryl acetoxystyryl sulfides useful as selective inhibitors of cyclooxygenase-2 relative to cyclooxygenase-1)

IT 313269-63-5P, (Z)-Styryl 2-acetoxystyryl sulfide 313269-64-6P,  
 (Z)-4-Fluorostyryl 2-acetoxystyryl sulfide 313269-65-7P,  
 (Z)-2-Chlorostyryl 2-acetoxystyryl sulfide 313269-66-8P,  
 (Z)-4-Chlorostyryl 2-acetoxystyryl sulfide 313269-72-6P,  
 (Z)-3-Acetoxystyryl 2-acetoxystyryl sulfide  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. of styryl acetoxystyryl sulfides useful as selective inhibitors of cyclooxygenase-2)

IT 313269-67-9P, (Z)-4-Bromostyryl 2-acetoxystyryl sulfide 313269-68-0P,  
 (Z)-4-Methylstyryl 2-acetoxystyryl sulfide 313269-69-1P,  
 (Z)-4-Ethylstyryl 2-acetoxystyryl sulfide 313269-70-4P,  
 (Z)-4-Pentylstyryl 2-acetoxystyryl sulfide 313269-71-5P,  
 (Z)-3-Hydroxystyryl 2-acetoxystyryl sulfide 313269-73-7P,  
 (Z)-4-Methoxystyryl 2-acetoxystyryl sulfide 313269-74-8P,  
 (Z)-4-Nitrostyryl 2-acetoxystyryl sulfide  
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. of styryl acetoxystyryl sulfides useful as selective inhibitors of cyclooxygenase-2)

L200 ANSWER 32 OF 36 CAPLUS COPYRIGHT 2003 ACS

AN 2000:757695 CAPLUS

DN 134:65940

TI Topical application of a selective cyclooxygenase inhibitor suppresses UVB mediated cutaneous inflammation

AU Wilgus, Traci A.; Ross, Mary S.; Parrett, Michelle L.; Oberyszyn, Tatiana M.

CS Department of Molecular Virology, Immunology and Medical Genetics, The College of Medicine, The Ohio State University, Columbus, OH, 43210, USA

SO Prostaglandins & Other Lipid Mediators (2000), 62(4), 367-384

CODEN: POLMFL; ISSN: 1098-8823

PB Elsevier Science Inc.

DT Journal

LA English

CC 1-7 (Pharmacology)

Section cross-reference(s): 8

AB This work compared the effects of topical **treatment** with **Celecoxib** (a specific COX [cyclooxygenase] 2 inhibitor) and ibuprofen (a nonspecific COX inhibitor) on the acute UVB-induced cutaneous inflammatory response in mice. The specific inhibition of COX-2 effectively reduced many parameters of UVB-mediated inflammation, including edema, dermal neutrophil infiltration and activation, plasma PGE2 levels and the formation of sunburn cells. By inhibiting this inflammatory response, topical **Celecoxib treatment** may ultimately be effective in preventing UVB-induced tumor development in the skin.

ST **skin inflammation** UV radiation **Celecoxib**  
 cyclooxygenase inhibitor; antiinflammatory **Celecoxib**  
 cyclooxygenase inhibitor skin UV radiation

IT Anti-inflammatory agents

**Dermatitis**

UV B radiation

(cyclooxygenase 2 inhibitor **Celecoxib** suppression of  
UVB-mediated cutaneous inflammation)

- IT Gene, animal  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(for cyclooxygenase 2; cyclooxygenase 2 inhibitor **Celecoxib** suppression of UVB-mediated cutaneous inflammation)
- IT 169590-42-5, **Celecoxib**  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(cyclooxygenase 2 inhibitor **Celecoxib** suppression of UVB-mediated cutaneous inflammation)
- IT 39391-18-9  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(cyclooxygenase-2, inhibitors; cyclooxygenase 2 inhibitor **Celecoxib** suppression of UVB-mediated cutaneous inflammation)

RE.CNT 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE

- (1) Baba, T; J Derma Science 1996, V12, P18 MEDLINE
- (2) Bayerl, C; Photoderm Photoimmuno Photomed 1995, V11, P149 MEDLINE
- (3) Bennett, A; Gut 1987, V28, P315 CAPLUS
- (4) Bennett, A; Prog Lipid Res 1986, V25, P539 CAPLUS
- (5) Black, A; Br J Clin Pharmacol 1978, V5, P431 CAPLUS
- (6) Black, A; Br J Clin Pharmacol 1982, V13, P351 CAPLUS
- (7) Boyne, A; Anal Biochem 1972, V46, P639 CAPLUS
- (8) Brash, D; Trends Genet 1997, V13, P410 CAPLUS
- (9) Buckman, S; Carcinogenesis 1998, V19, P723 CAPLUS
- (10) Cohen, D; Photochem Photobiol 1993, V57, P383 CAPLUS
- (11) Eberlein-Konig, B; Br J Dermatol 1998, V139, P415 CAPLUS
- (12) Eling, T; Pharmacol Ther 1992, V3, P261
- (13) Elmetts, C; Photochem Photobiol 1982, V6, P715
- (14) Fischer, S; Mol Carcinog 1999, V25, P231 CAPLUS
- (15) Fulton, A; Cancer Res 1984, V44, P2416 CAPLUS
- (16) Furstenberger, G; Carcinogenesis 1989, V10, P91 MEDLINE
- (17) Gallagher, R; Arch Dermatol 1995, V131, P157 MEDLINE
- (18) Giardello, F; Eur J Cancer 1995, V31A, P1071
- (19) Gierse, J; Biochem J 1999, V339, P607 CAPLUS
- (20) Goodwin, J; J Clin Immunol 1983, V3, P295 CAPLUS
- (21) Greaves, M; J Invest Dermatol 1970, V54, P365 CAPLUS
- (22) Gresham, A; Am J Physiol 1996, V270, PC1037 CAPLUS
- (23) Grewe, M; J Invest Dermatol 1993, V101, P528 CAPLUS
- (24) Hershman, H; Biochem Biophys Acta 1996, V1299, P125
- (25) Hla, T; Proc Natl Acad Sci USA 1992, V89, P7384 CAPLUS
- (26) Hruza, L; J Invest Dermatol 1993, V100, P355 CAPLUS
- (27) Jung, E; J Dermatol 1991, V18, P1 MEDLINE
- (28) Jung, T; Laryngoscope 1985, V95, P307 CAPLUS
- (29) Katiyar, S; Photochem Photobiol 1999, V69, P148 CAPLUS
- (30) Kripke, M; Immunol Rev 1984, V80, P87 MEDLINE
- (31) Kripke, M; J Dermatol 1991, V18, P429 MEDLINE
- (32) Kuwamoto, K; J Invest Dermatol 2000, V114, P241 CAPLUS
- (33) Ledwith, B; J Biol Chem 1997, V272, P3707 CAPLUS
- (34) Lupulescu, A; Prostaglandins, Leukotrienes and Ess Fatty Acids 1995, V54, P83
- (35) Maderazo, E; J Pharm Sci 1984, V73, P1403 CAPLUS
- (36) Maldve, R; Molec Carcinogen 1996, V17, P207 CAPLUS
- (37) Marks, R; Aust Paed J 1988, V24, P337 MEDLINE
- (38) Marks, R; Med J Aust 1990, V152, P62 MEDLINE
- (39) Marnett, L; Cancer Res 1992, V52, P5575 CAPLUS
- (40) Marshall, K; Am J Orthop 1999, V28, P19 MEDLINE
- (41) Mathur, G; J Invest Dermatol 1972, V58, P291 CAPLUS
- (42) McCormick, D; Br J Cancer 1983, V48, P859 CAPLUS

- (43) Mehlisch, D; Clin Pharmacol Ther 1997, V61, P195
- (44) Muller-Decker, K; Mol Carcinog 1995, V12, P31 MEDLINE
- (45) Muller-Decker, K; Molec Carcinogen 1995, V12, P31 MEDLINE
- (46) Narisawa, T; Carcinogenesis 1993, V14, P1493
- (47) Oates, J; N Engl J Med 1988, V319, P689 MEDLINE
- (48) Oberyszyn, T; Mol Carcinog 1998, V22, P16 CAPLUS
- (49) Parrett, M; Int J Oncol 1997, V10, P503 CAPLUS
- (50) Patrono, C; Kidney Int 1987, V32, P1 CAPLUS
- (51) Pentland, A; Carcinogenesis 1999, V20, P1939 CAPLUS
- (52) Pentland, A; J Clin Invest 1986, V77, P246 CAPLUS
- (53) Reddy, B; Cancer Res 1996, V56, P4566 CAPLUS
- (54) Reddy, B; Carcinogenesis 1993, V14, P1493 CAPLUS
- (55) Rigas, B; J Lab Clin Med 1993, V122, P518 MEDLINE
- (56) Ristimaki, A; J Biol Chem 1994, V269, P11769 CAPLUS
- (57) Rivas, J; J Leukoc Biol 1994, V56, P769 CAPLUS
- (58) Robertson, F; Cancer Lett 1998, V122, P165 CAPLUS
- (59) Sano, H; Cancer Res 1995, V55, P3785 CAPLUS
- (60) Savage, J; J Invest Dermatol 1993, V10, P532
- (61) Schwarz, T; Dermatologica 1985, V171, P450 CAPLUS
- (62) Seibert, K; Proc Natl Acad Sci USA 1994, V91, P12013 CAPLUS
- (63) Seibert, K; Proc Natl Acad Sci USA 1994, V91, P12013 CAPLUS
- (64) Simchowitz, L; Arthritis Rheum 1979, V22, P755 CAPLUS
- (65) Simon, L; Arthritis Rheum 1998, V41, P1591 CAPLUS
- (66) Smolen, J; Biochem Pharmacol 1980, V29, P533 CAPLUS
- (67) Snyder, D; J Invest Dermatol 1975, V64, P322 CAPLUS
- (68) Sontag, S; Drugs 1996, V32, P445
- (69) Soter, N; Semin Dermatol 1990, V9, P11 MEDLINE
- (70) Stern, M; Carcinogenesis 1998, V19, P125 CAPLUS
- (71) Trush, M; Food Chem Toxicol 1994, V32, P143 CAPLUS
- (72) Tsujii, M; Cell 1995, V83, P493 CAPLUS
- (73) Tsujii, M; Cell 1998, V93, P705 CAPLUS
- (74) Turner, R; J Rheumatol 1984, V11, P265 CAPLUS
- (75) Vane, J; Proc Natl Acad Sci USA 1994, V91, P2046 CAPLUS
- (76) Vile, G; Arch Biochem Biophys 1998, V359, P51 CAPLUS
- (77) Wahlberg, J; Contact Dermatitis 1993, V28, P141 MEDLINE
- (78) Wallace, J; Gastroenterol Clin North Am 1992, V21, PL631
- (79) Wu, K; J Lab Clin Med 1996, V128, P242 CAPLUS
- (80) Yamawaki, M; J Invest Dermatol 1997, V6, P716
- (81) Young, A; Photo-Dermat 1987, V4, P127 MEDLINE
- (82) Yuan, C; Cancer Res 2000, V60, P1084 CAPLUS

L200 ANSWER 33 OF 36 CAPLUS COPYRIGHT 2003 ACS

AN 2000:72484 CAPLUS

DN 132:87911

TI **Celecoxib** versus diclofenac in long-term management of  
rheumatoid arthritis: randomized double-blind comparison

AU Emery, Paul; Zeidler, Henning; Kvien, Tore K.; Guslandi, Mario; Naudin,  
Raphael; Stead, Helen; Verburg, Kenneth M.; Isakson, Peter C.; Hubbard,  
Richard C.; Geis, G. Steven

CS Department of Rheumatology and Rehabilitation, University of Leeds, Leeds,  
UK

SO Lancet (1999), 354(9196), 2106-2111

CODEN: LANCAO; ISSN: 0140-6736

PB Lancet Ltd.

DT Journal

LA English

CC 1-7 (Pharmacology)

AB Background: Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit  
cyclo-oxygenase (COX), which leads to suppression of COX-1-mediated prodn.  
of gastrointestinal-protective prostaglandins. Gastrointestinal injury is  
a common outcome. We compared the efficacy, safety, and tolerability of  
long-term therapy with **celecoxib**, a COX-1 sparing inhibitor of  
COX-2, with diclofenac, a non-specific COX inhibitor. Methods: 655  
patients with adult-onset rheumatoid arthritis of at least 6 mo' duration

were randomly assigned oral **celecoxib** 200 mg twice daily or diclofenac SR 75 mg twice daily for 24 wk. Anti-inflammatory and analgesic activity and tolerability were assessed at baseline, every 4 wk, and at week 24. We assessed gastrointestinal safety by upper-gastrointestinal endoscopy within 7 days of the last **treatment** dose at centers where the procedure was available. Anal. was by intention-to-treat. Findings: 430 patients underwent endoscopy (**celecoxib** n=212, diclofenac n=218). The two drugs were similar in management of rheumatoid arthritis pain and inflammation. Gastroduodenal ulcers were detected endoscopically in 33 (15%) patients **treated** with diclofenac and in eight (4%) in the **celecoxib** group ( $p<0.001$ ). The rate of withdrawal for any gastrointestinal-related adverse event, most commonly abdominal pain, **diarrhea**, and dyspepsia, was nearly three times higher in the diclofenac-**treated** group than in the **celecoxib** group (16 vs. 6%;  $p<0.001$ ). Interpretation: **Celecoxib** showed sustained anti-inflammatory and analgesic activity similar to diclofenac, with a lower frequency of upper gastrointestinal ulceration or gastrointestinal adverse events, and tolerability was better.

ST **celecoxib** diclofenac rheumatoid arthritis stomach ulcer

IT Antirheumatic agents

Dyspepsia

Ulcer

(efficacy and safety of **celecoxib** vs. diclofenac in long-term management of rheumatoid arthritis in humans)

IT 15307-86-5, Diclofenac 169590-42-5, **Celecoxib**

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(efficacy and safety of **celecoxib** vs. diclofenac in long-term management of rheumatoid arthritis in humans)

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE

- (1) ARA Glossary Committee; Dictionary of the Rheumatic Disease 1988, V1
- (2) Agrawal, N; Dig Dis Sci 1995, V40, P1125 MEDLINE
- (3) Akdamar, K; Gastrointest Endoscopy 1986, V32, P78 MEDLINE
- (4) Arnett, F; Arthritis Rheum 1988, V31, P315 MEDLINE
- (5) Barrier, C; Arthritis Rheum 1989, V32, P926 MEDLINE
- (6) Cooperating Clinics Committee of American Rheumatism Association; Arthritis Rheum 1965, V8, P302
- (7) Crofford, L; J Clin Invest 1994, V93, P1095 CAPLUS
- (8) Felson, D; Arthritis Rheum 1995, V38, P727 MEDLINE
- (9) Gabriel, S; Ann Intern Med 1991, V115, P787 MEDLINE
- (10) Gierse, J; Biochem J 1995, V305, P479 CAPLUS
- (11) Ihmaki, T; Scand J Gastroenterol 1979, V14, P801
- (12) Kargman, S; Am Gastroenterol Assoc 1996, V111, P445 CAPLUS
- (13) Kirwan, J; Br J Rheumatol 1986, V25, P206 MEDLINE
- (14) Kolodny, A; J Rheumatol 1988, V15, P1205 MEDLINE
- (15) Kujubu, D; J Biol Chem 1991, V266, P12866 CAPLUS
- (16) Laneuville, O; J Pharmacol Exp Ther 1994, V271, P927 CAPLUS
- (17) Langman, M; Lancet 1994, V343, P1075 MEDLINE
- (18) Masferrer, J; Proc Natl Acad Sci USA 1994, V91, P3228 CAPLUS
- (19) Needleman, P; Ann Rev Biochem 1986, V55, P69 CAPLUS
- (20) Penning, T; J Med Chem 1997, V40, P1347 CAPLUS
- (21) Roth, S; Clin Drug Invest 1995, V9, P171
- (22) Sano, H; J Clin Invest 1992, V89, P97 CAPLUS
- (23) Seibert, K; Proc Natl Acad Sci USA 1994, V91, P12013 CAPLUS
- (24) Silverstein, F; Ann Intern Med 1995, V123, P241 MEDLINE
- (25) Simon, L; Arthritis Rheum 1998, V41, P1591 CAPLUS
- (26) Singh, G; J Rheumatol 1998, V25(suppl 51), P8
- (27) Smith, W; Adv Immunol 1996, V62, P167 CAPLUS
- (28) Steinbrocker, O; JAMA 1949, V140, P659
- (29) Vane, J; Nat New Biol 1971, V231, P232 CAPLUS
- (30) Vane, J; Proc Natl Acad Sci USA 1994, V91, P2046 CAPLUS

- (31) Ward, J; Arthritis Rheum 1983, V26, P1303 MEDLINE  
(32) Xie, W; Proc Natl Acad Sci USA 1991, V88, P2692 CAPLUS

L200 ANSWER 34 OF 36 CAPLUS COPYRIGHT 2003 ACS

AN 1999:669180 CAPLUS

DN 132:160652

TI **Celecoxib**, a selective cyclooxygenase-2 inhibitor for the treatment of rheumatoid arthritis and osteoarthritis

AU Goldenberg, Marvin M.

CS Mount Sinai NYU Health, New York, NY, USA

SO Clinical Therapeutics (1999), 21(9), 1497-1513

CODEN: CLTHDG; ISSN: 0149-2918

PB Excerpta Medica

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

AB A review with 56 refs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs, despite their well-established assocn. with gastroduodenal injury. Recent discovery of the cyclooxygenase (COX) isoenzymes COX-1 and COX-2 has improved our knowledge of the action of NSAIDs. COX-1 is continuously expressed in almost all tissues, where it converts arachidonate to the prostaglandins (PGs) important in homeostatic function; COX-2 is present in immune cells, blood vessel endothelial cells, and synovial fibroblasts. Classic NSAIDs inhibit both COX isoenzymes by occupying the cyclooxygenase-active site, preventing access by arachidonic acid. In theory, a drug such as **celecoxib** that selectively inhibited COX-2 might block inflammation, pain, and fever while reducing the side effects (gastric erosions and ulcers) assocd. with inhibition of COX-1. In animal models of inflammation and pain, **celecoxib** has shown marked suppression of PG prodn. and inflammation compared with indomethacin, the std. COX-1/COX-2 inhibitor. In clin. trials, **celecoxib** dosed at 100, 200, and 400 mg BID was found to significantly reduce the signs and symptoms of rheumatoid arthritis (RA) and osteoarthritis. In one RA study, **celecoxib** was found to be as clin. effective as diclofenac after 24 wk of treatment; at the end of the study, gastroduodenal ulcers occurred significantly more frequently in the diclofenac group (15%) than in the **celecoxib** group (4%). In a 1-wk endoscopy study comparing **celecoxib** with naproxen and placebo, the incidence of gastric erosions/ulcers was significantly greater in the naproxen group than in the **celecoxib** or placebo group. The most common adverse effects of **celecoxib** in clin. studies were headache, diarrhea, abdominal discomfort, and dizziness. **Celecoxib** has shown significant equiv. anti-inflammatory and analgesic efficacy and has produced less endoscopically apparent gastrointestinal (GI) ulceration or erosion than have 3 classic NSAIDs. Whether it will have long-term GI adverse effects or interact with other medications to cause serious adverse responses (eg, increased GI bleeding or rash in conjunction with other sulfonamide-like drugs) is unknown and remains to be established.

ST review COX2 inhibitor **celecoxib** rheumatoid arthritis osteoarthritis

IT Analgesics

Antiarthritics

Antirheumatic agents

(COX-2 inhibitor **celecoxib** for rheumatoid arthritis and osteoarthritis treatment)

IT Prostaglandins

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(COX-2 inhibitor **celecoxib** for rheumatoid arthritis and osteoarthritis treatment)

IT Anti-inflammatory agents

(nonsteroidal; COX-2 inhibitor **celecoxib** for rheumatoid

arthritis and osteoarthritis treatment)

IT Digestive tract  
(toxicity; COX-2 inhibitor **celecoxib** for rheumatoid arthritis and osteoarthritis treatment)

IT Stomach, disease  
(ulcer; COX-2 inhibitor **celecoxib** for rheumatoid arthritis and osteoarthritis treatment)

IT **169590-42-5, Celecoxib**  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(COX-2 inhibitor **celecoxib** for rheumatoid arthritis and osteoarthritis treatment)

IT 39391-18-9, Cyclooxygenase  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(COX-2 inhibitor **celecoxib** for rheumatoid arthritis and osteoarthritis treatment)

RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE

- (1) Anderson, G; J Clin Invest 1996, V97, P2672 CAPLUS
- (2) Anon; FDC Reports 1998, V60, P3
- (3) Appelby, S; Biochem J 1994, V302, P723
- (4) Brooks, P; N Engl J Med 1991, V324, P1716 MEDLINE
- (5) Crofford, L; J Clin Invest 1994, V93, P1095 CAPLUS
- (6) Crofford, L; J Rheumatol 1997, V24(Suppl 49), P15
- (7) Cronstein, B; Annu Rev Pharmacol Toxicol 1995, V35, P449 CAPLUS
- (8) De Witt, D; Arch Biochem Biophys 1993, V306, P94 CAPLUS
- (9) Eberhart, C; Gastroenterology 1995, V109, P285 CAPLUS
- (10) Flower, R; Pharmacol Rev 1974, V26, P33 CAPLUS
- (11) Fries, J; Gastroenterology 1989, V96, P647 MEDLINE
- (12) Fu, J; J Biol Chem 1990, V265, P16737 CAPLUS
- (13) GD Searle & Co; Celebrex [package insert] 1999
- (14) Geis, G; Arthritis Rheum 1998, V41(Suppl 9), PS316
- (15) Gierse, J; Biochem J 1995, V305, P479 CAPLUS
- (16) Hawkey, C; Lancet 1999, V353, P307 CAPLUS
- (17) Hoff, T; FEBS Lett 1993, V320, P38 CAPLUS
- (18) Hubbard, R; Arthritis Rheum 1996, V39(Suppl 9), PS226
- (19) Hubbard, R; Arthritis Rheum 1997, V40(Suppl 9), PS51
- (20) Hubbard, R; J Invest Med 1996, V44, P293
- (21) Jones, D; J Biol Chem 1993, V268, P9049 CAPLUS
- (22) Karim, A; Arthritis Rheum 1998, V41(Suppl 9), PS315
- (23) Kosaka, T; Eur J Biochem 1994, V221, P889 CAPLUS
- (24) Kujubu, D; J Biol Chem 1991, V266, P12866 CAPLUS
- (25) Kurumbail, R; Nature 1996, V384, P644 CAPLUS
- (26) Laneuville, O; J Pharmacol Exp Ther 1994, V271, P927 CAPLUS
- (27) Lanza, F; Am J Gastroenterol 1993, V88, P1318 MEDLINE
- (28) Lanza, F; Arthritis Rheum 1997, V40(Suppl 9), PS93
- (29) Lee, S; J Biol Chem 1992, V267, P25934 CAPLUS
- (30) Marnett, L; Cancer Res 1992, V52, P5575 CAPLUS
- (31) Masferrer, J; Proc Natl Acad Sci USA 1992, V89, P3917 CAPLUS
- (32) Masferrer, J; Proc Natl Acad Sci USA 1994, V91, P3228 CAPLUS
- (33) McAdam, B; Proc Natl Acad Sci USA 1999, V96, P272 CAPLUS
- (34) Mingle-Gaw, L; Arthritis Rheum 1997, V40(Suppl 9), PS88
- (35) Needleman, P; Sci Med 1998, V1, P35
- (36) O'Banion, M; J Biol Chem 1991, V266, P23261 CAPLUS
- (37) O'Neill, G; Mol Pharmacol 1994, V45, P245 CAPLUS
- (38) Penning, T; J Med Chem 1997, V40, P1347 CAPLUS
- (39) Picot, D; Nature 1994, V367, P243 CAPLUS
- (40) Raz, A; Proc Natl Acad Sci USA 1989, V86, P1657 CAPLUS
- (41) Ristimaki, A; J Biol Chem 1994, V269, P11769 CAPLUS
- (42) Roth, G; Proc Natl Acad Sci USA 1975, V72, P3073 CAPLUS
- (43) Roth, S; Arch Intern Med 1996, V156, P1623 CAPLUS
- (44) Sano, H; J Clin Invest 1992, V89, P97 CAPLUS
- (45) Siebert, K; Proc Natl Acad Sci USA 1994, V91, P12013

- (46) Simon, L; Arthritis Rheum 1998, V41, P1591 CAPLUS  
 (47) Smith, W; Biochim Biophys Acta 1991, V1083, P1 CAPLUS  
 (48) Smith, W; Immunology 1996, V62, P167 CAPLUS  
 (49) Smith, W; Nature 1971, V231, P235  
 (50) The Cooperating Clinics Committee of the American Rheumatism Association;  
 Arthritis Rheum 1965, V8, P302  
 (51) Vane, J; Br J Rheumatol 1996, V35(Suppl 1), P1  
 (52) Vane, J; Nature 1971, V231, P232 CAPLUS  
 (53) Vane, J; Proc Natl Acad Sci USA 1994, V91, P2046 CAPLUS  
 (54) Whelton, A; J Clin Pharmacol 1991, V31, P588 MEDLINE  
 (55) Xie, W; Proc Natl Acad Sci USA 1991, V88, P2692 CAPLUS  
 (56) Zhao, S; Arthritis Rheum 1997, V40(Suppl 9), PS88

L200 ANSWER 35 OF 36 CAPLUS COPYRIGHT 2003 ACS

AN 1997:562995 CAPLUS

DN 127:225303

TI Immunosuppressive combinations containing a cyclooxygenase-2 inhibitor and  
 a leukotriene A4 hydrolase inhibitor

IN Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary

PA G.D. Searle & Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson,  
 Gary

SO PCT Int. Appl., 77 pp.

' CODEN: PIXXD2

DT Patent

LA English

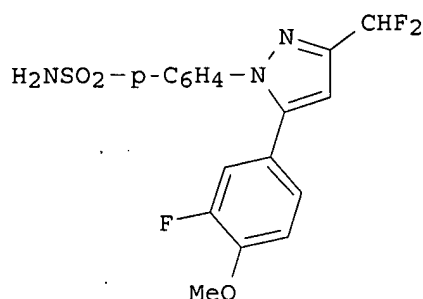
IC ICM A61K045-06

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 28

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9729774	A1	19970821	WO 1997-US1421	19970211
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,				
	DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC,				
	LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,				
	RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN,				
	YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,				
	IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML,				
	MR, NE, SN, TD, TG				
	CA 2246336	AA	19970821	CA 1997-2246336	19970211
	AU 9719525	A1	19970902	AU 1997-19525	19970211
	EP 880363	A1	19981202	EP 1997-907545	19970211
	EP 880363	B1	20020911		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	JP 2001506574	T2	20010522	JP 1997-529358	19970211
	AT 223732	E	20020915	AT 1997-907545	19970211
	ES 2183140	T3	20030316	ES 1997-907545	19970211
	US 6407140	B1	20020618	US 2000-489311	20000121
	US 2003004191	A1	20030102	US 2002-137231	20020502
PRAI	US 1996-600655	A1	19960213		
	WO 1997-US1421	W	19970211		
	US 2000-489311	A3	20000121		
OS	MARPAT 127:225303				
GI					



- AB Immunosuppressant compns. contg. a combination of a cyclooxygenase-2 inhibitor (which inhibits conversion of arachidonic acid to prostaglandins) and a LTA4 hydrolase inhibitor are useful in reducing recipient rejection of transplanted organs and for treatment of autoimmune diseases. Thus, F2CHCO2Et reacted with 3-fluoro-4-methoxyacetophenone to form 4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)butane-1,3-dione, which was condensed with 4-sulfonamidophenylhydrazine-HCl to produce the cyclooxygenase-2 inhibitor I. A formulation was prepd. contg. 350 mg I and 700 mg 3-[N-methyl-N-[3-[(4-phenylmethyl)phenoxy]propyl]amino]propanoic acid (LTA4 hydrolase inhibitor).
- ST immunosuppressant cyclooxygenase inhibitor; leukotriene hydrolase inhibitor transplant rejection
- IT Kidney, disease  
(Goodpasture's syndrome; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)
- IT Thyroid gland, disease  
(autoimmune thyroiditis; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)
- IT **Dermatitis**  
(contact; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)
- IT Allergy inhibitors  
Allergy inhibitors  
(delayed hypersensitivity; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)
- IT Respiratory tract  
(disease, hypersensitivity; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)
- IT Kidney, disease  
(glomerulonephritis; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)
- IT Transplant and Transplantation  
(graft-vs.-host reaction; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)
- IT Anemia (disease)  
(hemolytic, autoimmune; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)
- IT Allergy  
(hypersensitivity, respiratory tract; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)
- IT Addison's disease  
(idiopathic; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)
- IT Allergy  
(immediate hypersensitivity; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)
- IT Allergy inhibitors  
Anti-inflammatory agents  
Antiasthmatics

Autoimmune disease  
 Encephalomyelitis  
 Graves' disease  
 Immunosuppressants  
 Meningitis  
 Myasthenia gravis  
 Sjogren's syndrome  
 Transplant rejection  
 Urticaria  
 (immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Granuloma  
 (inhibitors; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Connective tissue  
 (mixed connective tissue disease; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Lung, disease  
 (pneumonitis, hypersensitive; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Shock (circulatory collapse)  
 (septic; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Platelet (blood)  
 (thrombocytopenia; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Purpura (disease)  
 (thrombocytopenic, autoimmune; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Thyroid gland, disease  
 Thyroid gland, disease  
 (thyroiditis; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT 39391-18-9  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (2, inhibitors; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT 142259-95-8, RP-64966 179021-09-1 179021-10-4 179022-08-3  
 186901-93-9 186901-94-0 186901-95-1 186901-96-2 186901-97-3  
 186901-98-4 194997-63-2  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (LTA4 hydrolase inhibitor; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT 71125-38-7, Meloxicam 80937-31-1, Flosulide 88149-94-4, DuP 697  
 123653-11-2, NS-398 162011-83-8 169590-41-4 **169590-42-5**  
 170569-86-5 177660-77-4 177660-80-9 177660-88-7 181695-76-1  
 185344-61-0 194997-65-4 194997-66-5 194997-67-6  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (cyclooxygenase-2 inhibitor; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT **162011-90-7**  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT 99-91-2 321-28-8, 2-Fluoroanisole 383-63-1, Ethyl trifluoroacetate  
 454-31-9, Ethyl difluoroacetate 27918-19-0, 4-Sulfonamidophenylhydrazine hydrochloride  
 RL: RCT (Reactant); RACT (Reactant or reagent)

(immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)  
 IT 455-91-4P 18931-60-7P 170570-77-1P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)  
 IT 90119-07-6, Leukotriene A4 hydrolase  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (inhibitors; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

L200 ANSWER 36 OF 36 CAPLUS COPYRIGHT 2003 ACS

AN 1997:557660 CAPLUS

DN 127:239120

TI Compositions comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection

IN Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary

PA G.D. Searle & Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary

SO PCT Int. Appl., 63 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K045-06

ICS A61K031-00; A61K031-10; A61K031-18; A61K038-13

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1, 2

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9729775	A1	19970821	WO 1997-US1422	19970211
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2246356	AA	19970821	CA 1997-2246356	19970211
	AU 9722500	A1	19970902	AU 1997-22500	19970211
	EP 880362	A1	19981202	EP 1997-905663	19970211
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	JP 2000505445	T2	20000509	JP 1997-529359	19970211
	US 6172096	B1	20010109	US 1998-75633	19980511
PRAI	US 1996-600580	A1	19960213		
	WO 1997-US1422	W	19970211		
OS	MARPAT 127:239120				
AB	<b>Treatment</b> with a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist is described as being useful in reducing recipient rejection of transplanted organs and for <b>treatment</b> of autoimmune diseases.				
ST	immunodepressant transplant cyclooxygenase2 inhibitor leukotrieneB4 antagonist				
IT	Kidney, disease (Goodpasture's syndrome; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)				
IT	Leukocyte (activation of, inhibitors of; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)				
IT	Anti-inflammatory agents				

Autoimmune disease  
Encephalomyelitis  
Granuloma  
Immunosuppressants  
Meningitis  
Urticaria

(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Myasthenia gravis  
Sjogren's syndrome  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT **Dermatitis**  
(contact; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Drug delivery systems  
(emulsions; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Kidney, disease  
(glomerulonephritis; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Transplant and Transplantation  
(graft-vs.-host reaction; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Anemia (disease)  
(hemolytic; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Lung, disease  
(hypersensitivity pneumonitis; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Addison's disease  
(idiopathic; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Leukotriene receptors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(leukotriene B4, antagonists; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Drug delivery systems  
(oral; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Shock (circulatory collapse)  
(septic; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Purpura (disease)  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(thrombocytopenic, autoimmune; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Thyroid gland, disease  
Thyroid gland, disease  
(thyroiditis; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 39391-18-9  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(2, antagonists; compns. comprising a cyclooxygenase-2 inhibitor and a

leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 127378-46-5, CI 987  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (CI 987; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 170569-86-5P 195061-35-9P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 32222-06-3, Calcitriol 59865-13-3, Cyclosporin a 60940-34-3, Ebselen 71125-38-7, Meloxicam 79217-60-0, Cyclosporin 80937-31-1, Flosulide 85259-71-8, BAY 0-8276 88149-94-4, Dup 697 93014-16-5 101910-24-1, PF-5901 110501-66-1, TMK-688 111908-95-3, SK&F-104493 117423-74-2, LY 223982 117423-95-7, LY 213024 117690-79-6, LY-255283 118414-82-7, MK-886 119261-58-4, TEI 1338 120072-59-5, SC-41930 123653-11-2, NS-398 128253-31-6, Bay-x-1005 130211-75-5, T-757 132734-43-1, LY 233569 133430-69-0, ETH-615 134578-96-4, ONO LB457 135199-82-5, LY 264086 135893-33-3, PF 10042 136326-31-3, WAY 121006 141059-52-1, SC-51146 141748-00-7, RP 69698 141835-49-6, RG 14893 142422-79-5, RP 66153 146461-98-5, SM 15178 147030-01-1, MK-591 147398-01-4, CGS-25019C 147432-77-7, Ontazolast 150399-22-7, SB-201993 153034-77-6, LY 292728 153633-01-3, SC-53228 154413-61-3, SB-209247 158081-99-3, Pfizer 105696 161172-51-6, LY-293111 162011-83-8  
**162011-90-7** 162153-46-0, SC 52798 169590-41-4  
**169590-42-5** 177660-77-4 177660-80-9 177660-92-3  
 180208-37-1, SB-201146 181695-72-7 185344-51-8 185344-55-2  
 186912-85-6, ONO-LB-448 186912-92-5, RP 66364 186912-94-7, SC-50505 195061-34-8 195215-25-9, BPC 15 195215-47-5, MNX 160 195215-53-3, S 2474 195215-55-5, SR 2566  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 99-91-2, 4'-Chloroacetophenone 383-63-1, Ethyl trifluoroacetate 454-31-9, Ethyl difluoroacetate 27918-19-0, 4-Sulfonamidophenyl hydrazine hydrochloride  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 455-91-4P, 3'-Fluoro-4'-methoxyacetophenone 18931-60-7P 170570-77-1P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

- AB The present invention provides methods for **treating** intestinal fluid loss, whooping cough, anthrax, and conditions associated with smooth muscle contraction. The present invention also provides methods for inhibiting adenylate cyclase in vivo and in vitro.
- SUMM [0003] Diarrheal diseases in humans and non-human animals can be caused by several types of pathogens, including viruses, bacteria, parasites, and rotaviruses. The most prevalent are the bacteria *Escherichia coli* and *Vibrio cholerae*. Diarrheal diseases are a prevalent cause of morbidity and mortality in less developed countries. These diseases also afflict populations in developed countries. For example, each year in the US over 200,000 children 5 years and younger are hospitalized with acute diarrheal diseases. The infectious **diarrheas** are the leading cause of morbidity and mortality worldwide a common class of illness in the United States.
- SUMM [0004] Due to its many causes, acute infectious **diarrhea** can occur more than once in the same person, and, therefore, it is unlike most chronic conditions which typically occur once. Unlike other digestive diseases, infectious **diarrheas** are communicable via person-to-person contact or through contaminated food or water and can spread endemically or in epidemics through households, schools, day-care centers, nursing homes, and communities. Diarrheal diseases also pose a serious challenge in the raising of non-human animals in the farming industry, particularly with young calves and pigs.
- SUMM [0005] The present invention represents an advance in the art of **treating** intestinal fluid loss in a subject. The invention provides methods for **treating** intestinal fluid loss in a subject. The method includes administering to a subject who has or is at risk of developing intestinal fluid loss a composition that includes an effective amount of heterocycle-containing compounds such as a heterocycle derivative, for instance a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. In some embodiments of this aspect of the invention the fluid loss is not associated with a pathogen polypeptide having ADP-ribosylation activity, and in other aspects the intestinal fluid loss is associated with a pathogen polypeptide having ADP-ribosylation activity.
- SUMM [0008] The present invention further provides a method for **treating** whooping cough in a subject, including administering to a subject who has or is at risk of developing whooping cough a composition that includes an effective amount of a heterocycle-containing compound.
- SUMM [0009] The present invention also provides a method for **treating** anthrax in a subject, including administering to a subject who has or is at risk of developing anthrax a composition that includes an effective amount of a heterocycle-containing compound.
- DRWD [0021] FIG. 11. **Celecoxib** reduced CT-induced fluid accumulation in murine intestinal loops. CT, cholera toxin; CT + **celecoxib** in loop, mice challenged with cholera toxin and two 80 microgram (mg) doses of **celecoxib** (one injected into the intestinal lumen at the time of challenge with CT, the second injected intraperitoneally two hours later); CT +**celecoxib** IP only, mice challenged with cholera toxin and two 80 microgram (.mu.g) doses of **celecoxib** (one injected intraperitoneally at the time of challenge with CT, the second injected intraperitoneally two hours later). The vertical bars indicate one standard error above or below the mean. The asterisks indicate a significant difference from the positive control group as determined by the Tukey test (P<0.05).
- DRWD [0022] FIG. 12. Effect of imidazole (2.7 mmoles), PGE.sub.2-Histidine

adduct (52 .mu.moles) and **celecoxib** (0.52 mmoles) on the enzyme Adenylate Cyclase (4.6 nmoles). Blank has no enzyme and inhibitors, while Enzyme (E) has only enzyme and no inhibitors. Enzyme containing specific inhibitors are represented as E+imidazole, E+PGE.sub.2-Histidine and E+**celecoxib**. Significant difference from the control value (E) is indicated by \*P.ltoreq.0.05 and \*P.ltoreq.0.001 as determined by Student's t-test.

DRWD [0023] FIG. 13. Fluid accumulation in Cholera toxin challenged murine intestinal ligated loops **treated** with the COX-1 inhibitor SC-560. n, number of animals; CT 1 .mu.g/loop, 1 microgram of cholera toxin added to each loop; CT +9 nM SC-560, 1 microgram of cholera toxin and 9 nanomolar SC-560 added to each loop The asterisks indicate a significant difference from the positive control (CT) as determined by the Tukey test.

DRWD [0025] FIG. 15. IC.sub.50 of **celecoxib** for adenylate cyclase.

DETD [0039] **rofecoxib** (available under the trade designation **VIOXX**, from Merck & Co., Whitehouse Station, N.Y.), which has the following structure: ##STR9##

DETD [0040] **celecoxib** (available under the trade designation **CELEBREX**, from Searle and Co., Skokie, Ill.), which has the following structure: ##STR10##

DETD [0049] Typically, the compositions of the invention will be administered from about 1 to about 5 times per day. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the subject **treated** and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound. The amount of heterocycle-containing compound in such therapeutically useful compositions is such that the dosage level will be effective to prevent or suppress the condition the subject has or is at risk for.

DETD [0055] The present invention is further directed to methods for **treating** certain conditions in a subject as well as various in vitro methods. The conditions include, for instance, intestinal fluid loss, whooping cough, anthrax, and smooth muscle contraction, and are described in greater detail herein. The methods include administering a composition including a heterocycle-containing compound to a subject who is at risk of developing or has developed one of the conditions. As used herein, the term "subject" includes humans, agriculturally important animals such as cows, pigs, poultry, sheep, and horses, as well as other animals (for instance, mice, rats, dogs, cats, and rabbits) that can be used as animal models in the study of the conditions described herein.

DETD [0056] **Treatment** of the conditions described herein can be prophylactic or, alternatively, can be initiated after the development of a condition described herein. **Treatment** that is prophylactic, for instance, initiated before a subject manifests symptoms of a condition described herein and/or before exposure to a pathogen associated with (i.e., caused by) one of the conditions described herein, is referred to herein as **treatment** of a subject that is "at risk" of developing the condition. Accordingly, administration of a composition can be performed before, during, or after the occurrence of the conditions described herein. **Treatment** initiated after the development of a condition may result in decreasing the severity of the symptoms of one of the conditions, or completely removing the symptoms. Non-limiting examples of subjects particularly suited to receiving the composition are those undergoing antibiotic **treatment**, in particular the elderly and the very young, preferably antibiotic **treatment** that has been associated with antibiotic-associated colitis, those traveling to a location where pathogens causing intestinal fluid loss are endemic (for instance, those likely to contract Traveler's **diarrhea**), and those infected with HIV.

DETD [0057] A composition that is administered to a subject who has or is at risk of developing a condition described herein includes an effective

amount of a heterocycle-containing compound, preferably, a heterocycle derivative, and for certain embodiments, a diphenyl-substituted heterocycle derivative and/or a prostaglandin analog. As used herein, an "effective amount" is an amount effective to decrease or prevent (for prophylactic **treatment**) in a subject the symptoms associated with a condition described herein.

DETD [0058] An aspect of the invention is directed to a method of **treating** intestinal fluid loss in a subject. As used herein, the term "intestinal fluid loss" refers to various types of **diarrheas** (i.e., an increased frequency and/or liquidity of fecal discharges when compared to normal individuals with formed stools). Intestinal fluid loss can result from, for instance, increased fluid secretion (e.g., water and/or electrolytes) from intestinal cells into the intestinal lumen, decreased absorption of water and/or electrolytes from the intestinal lumen, and/or movement of blood and mucus into the intestinal lumen. Intestinal fluid loss is usually associated with the presence of a pathogen, although foods having hyperosmolality can elicit hypersecretion of water and electrolytes. This is in contrast to idiopathic inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis. The latter chronic diseases are not associated with any particular infectious agent and result from uncontrolled inflammation of the colon and other regions of the intestinal tract.

DETD [0059] Pathogens that cause intestinal fluid loss include pathogens that are present in the intestinal lumen (for instance, *Vibrio cholerae*) or present in intestinal cells (for instance, *Shigella*), and pathogens that may not be present in the intestinal lumen or in intestinal cells (for instance, HIV). Examples of pathogens include viruses, parasites, and bacteria (see, for instance, Cotran et al., Robbins Pathologic Basis of Disease, 5.sup.th ed., W.B. Sanders Co., Philadelphia, pp. 328-335 (1994)). Intestinal fluid loss caused by pathogens is referred to in the art in numerous ways, including, for instance, **diarrhea**, dysentery, Travelers' **diarrhea**, and scours (in calves).

DETD [0066] In some aspects of the invention, when the intestinal fluid loss is not associated with a pathogen polypeptide having ADP-ribosylation activity (e.g., the intestinal fluid loss is associated with antibiotic **treatment**, the age of the subject, and/or infection by, for instance, a virus, a bacterium, a parasite, or a combination thereof), the heterocycle-containing compound present in the composition is a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. Examples of diphenyl heterocycles that can be used in this aspect of the invention include **celecoxib**, **rofecoxib**, SC-560, and DuP-697. Examples of prostaglandin analogs that can be used in this aspect of the invention include PGE.sub.2-histidine and PGE.sub.2-imidazole. Optionally, the composition can include, in addition to these heterocycle derivatives, an effective amount of metronidazole (available under the trade designation FLAGYL, from Searle and Co.) and/or an effective amount of indomethacin (available under the trade designation INDOCIN, from Merck & Co.). Of these two, metronidazole is preferred.

DETD [0067] In another aspect of the invention, when the intestinal fluid loss is associated with a pathogen polypeptide having ADP-ribosylation activity (e.g., the intestinal fluid loss is associated with *V. cholerae*, ETEC, or a combination thereof), the heterocycle-containing compound present in the composition is preferably an unsubstituted heterocyclic compound (e.g., imidazole), a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. More preferably, the heterocycle-containing compound present in the composition can be an unsubstituted heterocyclic compound (e.g., imidazole), a diphenyl heterocycle derivative, or a combination thereof. Examples of diphenyl heterocycles that can be used in this aspect of the invention include **rofecoxib**, SC-560, DuP-697, and in some embodiments, **celecoxib**. Preferably, the compositions do not include **celecoxib** for this method. Examples of a prostaglandin

analog that can be used in some embodiments of this aspect of the invention include PGE.sub.2-imidazole and PGE.sub.2-histidine. Compositions useful in this method can include an effective amount of metronidazole and/or an effective amount of indomethacin. Of these two, metronidazole is preferred.

DETD [0068] The invention is further directed to a method of **treating** whooping cough in a subject. Whooping cough is a disease of the respiratory tract caused by Bordetella pertussis. After exposure to B. pertussis, cells of the respiratory tract have increased cAMP levels. The method includes administering to a subject who has or is at risk of developing whooping cough a composition that includes an effective amount of a heterocycle-containing compound. The heterocycle-containing compound present in the composition is preferably an unsubstituted heterocyclic compound (e.g., imidazole), a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. The heterocycle-containing compound present in the composition is more preferably a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. Optionally, the composition can include, in addition to, these preferred heterocycle derivatives, an effective amount of metronidazole and/or indomethacin. Of these two, metronidazole is preferred.

DETD [0069] Another aspect of the invention is directed to a method for **treating** anthrax in a subject. Anthrax is an often fatal disease caused by Bacillus anthracis. One factor expressed by B. anthracis that is important in causing disease is edema factor, an adenylate cyclase which causes tissue edema by increasing cAMP levels. The method includes administering to a subject who has or is at risk of developing anthrax a composition comprising an effective amount of a heterocycle-containing compound. The heterocycle-containing compound present in the composition is preferably an unsubstituted heterocyclic compound (e.g., imidazole), a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. The heterocycle-containing compound present in the composition is more preferably a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. The heterocycle-containing compound present in the composition is more preferably a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. Optionally, the composition can include, in addition to, these preferred heterocycle derivatives, an effective amount of metronidazole and/or indomethacin. Of these two, metronidazole is preferred.

DETD [0072] The method for inhibiting adenylate cyclase in vivo includes contacting a cell that has been removed from a subject or is in a subject with a composition that includes an amount of a heterocycle derivative effective to inhibit the generation of cAMP from ATP. The cell includes adenylate cyclase and a pathogen polypeptide having ADP-ribosylation activity. Several conditions are associated with excessive adenylate cyclase activity and include, for instance, intestinal fluid loss as in diarrheal disease, tracheal and bronchial edema as in whooping cough, and pulmonary, gastrointestinal, and disseminated edema as in anthrax. Such conditions are described herein. The methods to inhibit adenylate cyclase can be used to **treat** such conditions.

DETD [0075] For methods of inhibiting adenylate cyclase, the heterocycle-containing compound present in the composition is preferably an unsubstituted heterocyclic compound (e.g., imidazole), a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. More preferably, the heterocycle-containing compound present in the composition can be an unsubstituted heterocyclic compound (e.g., imidazole), a diphenyl heterocycle derivative, or a combination thereof. Examples of diphenyl heterocycles that can be used in this aspect of the invention include **rofecoxib**, SC-560, DuP-697, and in some embodiments, **celecoxib**. Preferably, methods for inhibiting adenylate cyclase include **celecoxib** and DuP-697. Compositions useful in this method can include an effective amount of metronidazole

SUMM There are drugs that can be helpful in controlling Crohn's disease, but at present there is no cure. **Treatment** is aimed at correcting nutritional deficiencies, controlling inflammation, relieving the symptoms of abdominal pain, **diarrhea**, and **rectal bleeding**. Drugs known to be used for this condition can help, but side effects can be deleterious. Surgeries that may be performed to alleviate symptoms include the removal of inflamed areas, draining of abscesses, and bowel resection.

SUMM Mycobacterium paratuberculosis is an obligate pathogen; that is, it cannot multiply outside the cells of animals. It is known to be present in a wide variety of animals, including primates and humans. The best-studied animal paratuberculosis is bovine Johne's disease (BJD), a disease that causes chronic **diarrhea**, weight loss, and malnutrition in cattle and affects up to 25% of the dairy cattle in the United States. Cows infected with BJD are known to secrete Mycobacterium paratuberculosis in their milk, which is not destroyed by standard milk pasteurization methods, but only by ultrapasteurization. This bacterium has also been cultured from a municipal water supply in the United States.

SUMM A further object is to provide a composition and method for **treating** patients shown by the screening method to be infected with Mycobacterium paratuberculosis.

SUMM These objects and others are attained by the present invention, a composition and associated methods for detecting and **treating** a M. para. infection such as Crohn's disease in a human and for predicting a genetic predisposition thereto.

SUMM An embodiment of the **treatment** composition of the present invention comprises at least one antibiotic effective in the eradication of M. paratuberculosis.

SUMM In an embodiment of the **treatment** method, the effective antibiotic is administered to a patient having been found positive for M. paratuberculosis by the serologic method of the invention.

DETD The data also support an improved serologic kit comprising the composition of the invention to provide earlier diagnosis and better **treatment** of Crohn's disease.

DETD With the indication that Crohn's disease is at least in part caused by the presence of M. paratuberculosis, a **treatment** regimen including an administration of antituberculosis drugs was proposed. However, this bacterium is known to be resistant to most of these drugs. An in vitro study was performed to evaluate seven anti-TB drugs against M. para. isolated from resected tissue of CD patients using the Bactec system, which is known in the art, and the results are given in Table 2.

DETD Twenty-nine CD patients who tested serologically positive for M. para. were selected for rifabutin and macrolide antibiotic therapy (RMAT) for a duration of 6 months to 1 year based upon their overall response to the **treatment**. The regimen included 250 mgm po bid clarithromycin, 150 mgm 1 po bid rifabutin, and 200 mgm po qd of a probiotic containing equal amounts of Lactobacillus acidophilus and Lactobacillus rhamnosus.

DETD After 3 months all the patients were assessed to determine overall response to the **treatment**. 28% (8/29) of the patients achieved a state of clinical remission (as defined by the CDAI criteria with a score <150) while being off all other medications. The majority of these patients had acute presentation of CD when placed on RMAT. 31% (9/29) of the patients were not in clinical remission but experienced significant improvements as they discontinued the use of all other Crohn's medications. 28% (8/29) of the patients noticed some improvements on

RMAT but were still using traditional medications, such as sulfasalazine and corticosteroids. 14% (4/29) were nonresponders, since they were unable to tolerate the RMAT medications and discontinued therapy. These findings support the use of RMAT in the **treatment** of CD.

DETD The patient demonstrated significant healing (80%) of an ulcer seen in the ileum by endoscopy following a regimen of 250 mg clarithromycin twice a day and 150 mg rifabutin daily. The patient became asymptomatic in 2 weeks, and a followup endoscopy was performed after completing 1 month of **treatment**. The 4-cm ulcer had reduced in size to 1 cm, with excellent reepithelialization from the edge of the ulcer inward. The remaining ileum to 120 cm was normal. The patient has remained symptom-free and continues on the antibiotic regimen.

DETD As this study was continued, 35 patients with CD were being **treated** with RMAT. 37% (13/35) of the patients developed a serum sickness-like illness during the first 4-6 weeks of **treatment**. The patients experienced flu-like symptoms such as fever, chills, moderate to severe arthralgia, back pain, anorexia, and **fatigue**. These symptoms generally lasted for a full week and dissipated over the following 3 weeks. With each patient, a majority of symptoms stopped within the first month of **treatment**. It was also found that these symptoms responded well to Cox-2 inhibitors (**celecoxib** --200 mgm po qd) with no adverse effects or worsening of colitis noted during **treatment**. These observations suggest that the Cox-2 inhibitors may help in controlling the initial side effects of RMAT. It is also thought that this serum sickness may be a Jarisch-Herxheimer reaction in response to the antimicrobial therapy.

DETD Current hypotheses are being investigated regarding the causative agent(s) of Crohn's disease. While many workers in the field have become convinced of the involvement of M. para., it may well turn out that this bacterium is but one of a number of pathogenic agents. Therefore, the regimen proposed herein preselects patients for antibiotic **treatment** by the detecting method of the present invention, the combined p35/p36 serological test, patients testing negative for M. para. being less likely to experience alleviation of CD symptoms under the antibiotic regimen.

DETD It may be appreciated by one skilled in the art that additional embodiments may be contemplated, including other recombinant clones chosen from the M. paratuberculosis genomic library and other antibiotic regimens for the **treatment** of bacteria-positive CD patients.

ACCESSION NUMBER: 2001:167903 USPATFULL

TITLE: Crohn's disease diagnostic and **treatment** methods and compositions

INVENTOR(S): Shafran, Ira, 1316 Greencove Rd., Winter Park, FL, United States 32789

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6297015	B1	20011002
APPLICATION INFO.:	US 1999-404095		19990923 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-101579P	19980924 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Le, Long V.	
ASSISTANT EXAMINER:	Cook, Lisa V	
LEGAL REPRESENTATIVE:	Allen, Dyer, Doppelt, Milbrath & Gilchrist, P.A.	
NUMBER OF CLAIMS:	3	
EXEMPLARY CLAIM:	1	
LINE COUNT:	362	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		

n complex to the antigen

composition, wherein the bound antibody-antigen complex detects a presence of Mycobacterium avium ss. paratuberculosis, and thus indicates a presence of Crohn's disease; administering a regimen of an antibiotic effective in and sufficient for eradicating a presence of Mycobacterium paratuberculosis; and administering a regimen of a probiotic and a specific carbohydrate diet.

9. The method recited in claim 1, further comprising the steps, following the administering step, of: determining whether a **treated** patient is experiencing a serum sickness-like illness; and if the determining step is positive, **treating** the patient with a Cox-2 inhibitor.

10. The method recited in claim 9, wherein the Cox-2 inhibitor comprises **celecoxib**.

11. The method recited in claim 10, wherein the **celecoxib** is administered in an oral dose of 200 mgm once per day.

12. A method for **treating** a human patient suspected of having Crohn's disease comprising the steps of: screening for Crohn's disease by performing an ELISA analysis for serum antibodies to Mycobacterium avium subspecies paratuberculosis (MAP); and for patients screening positive for MAP, administering a regimen of an antibiotic effective in and sufficient for eradicating a presence of Mycobacterium paratuberculosis.

IT 54-85-3, Isoniazid 57-92-1, Streptomycin, biological studies 74-55-5, Ethambutol 98-96-4, Pyrazinamide 8063-07-8, Kanamycin 13292-46-1, Rifampicin 72559-06-9, Rifabutin 81103-11-9, Clarithromycin **1695 90-42-5**, Celecoxib

(antibiotic-based Crohn's disease treatment method, and Mycobacterium avium paratuberculosis-based diagnostic method)

ACCESSION NUMBER: 2002:336847 USPATFULL  
TITLE: Crohn's disease **treatment** methods  
INVENTOR(S): Shafran, Ira, Winter Park, FL, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002192201	A1	20021219
APPLICATION INFO.:	US 2002-165034	A1	20020607 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-968681, filed on 1 Oct 2001, PENDING Continuation-in-part of Ser. No. US 1999-404095, filed on 23 Sep 1999, GRANTED, Pat. No. US 6297015		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-101579P	19980924 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Jacqueline E. Hartt, Allen, Dyer, Doppelt, Milbrath & Gilchrist, P.A., 255 South Orange Avenue, Suite 1401, P.O. Box 3791, Orlando, FL, 32802-3791	
NUMBER OF CLAIMS:	19	
EXEMPLARY CLAIM:	1	
LINE COUNT:	465	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		

n complex to the antigen

composition, wherein the bound antibody-antigen complex detects a presence of Mycobacterium avium ss. paratuberculosis, and thus indicates a presence of Crohn's disease; administering a regimen of an antibiotic effective in and sufficient for eradicating a presence of Mycobacterium paratuberculosis; and administering a regimen of a probiotic and a specific carbohydrate diet.

9. The method recited in claim 1, further comprising the steps, following the administering step, of: determining whether a **treated** patient is experiencing a serum sickness-like illness; and if the determining step is positive, **treating** the patient with a Cox-2 inhibitor.

10. The method recited in claim 9, wherein the Cox-2 inhibitor comprises **celecoxib**.

11. The method recited in claim 10, wherein the **celecoxib** is administered in an oral dose of 200 mgm once per day.

12. A method for **treating** a human patient suspected of having Crohn's disease comprising the steps of: screening for Crohn's disease by performing an ELISA analysis for serum antibodies to Mycobacterium avium subspecies paratuberculosis (MAP); and for patients screening positive for MAP, administering a regimen of an antibiotic effective in and sufficient for eradicating a presence of Mycobacterium paratuberculosis.

IT 54-85-3, Isoniazid 57-92-1, Streptomycin, biological studies 74-55-5, Ethambutol 98-96-4, Pyrazinamide 8063-07-8, Kanamycin 13292-46-1, Rifampicin 72559-06-9, Rifabutin 81103-11-9, Clarithromycin 1695 90-42-5, Celecoxib

(antibiotic-based Crohn's disease treatment method, and Mycobacterium avium paratuberculosis-based diagnostic method)

ACCESSION NUMBER: 2002:336847 USPATFULL  
TITLE: Crohn's disease **treatment** methods  
INVENTOR(S): Shafran, Ira, Winter Park, FL, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002192201	A1	20021219
APPLICATION INFO.:	US 2002-165034	A1	20020607 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-968681, filed on 1 Oct 2001, PENDING Continuation-in-part of Ser. No. US 1999-404095, filed on 23 Sep 1999, GRANTED, Pat. No. US 6297015		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-101579P	19980924 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Jacqueline E. Hartt, Allen, Dyer, Doppelt, Milbrath & Gilchrist, P.A., 255 South Orange Avenue, Suite 1401, P.O. Box 3791, Orlando, FL, 32802-3791	
NUMBER OF CLAIMS:	19	
EXEMPLARY CLAIM:	1	
LINE COUNT:	465	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		

14. The method recited in claim 13, wherein the Cox-2 inhibitor comprises **celecoxib**.

15. The method recited in claim 13, wherein the **celecoxib** is administered in an oral dose of 200 mgm once per day.

ACCESSION NUMBER: 2002:198264 USPATFULL  
TITLE: Crohn's disease **treatment** methods  
INVENTOR(S): Shafran, Ira, Winter Park, FL, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002106357	A1	20020808
APPLICATION INFO.:	US 2001-968681	A1	20011001 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-101579P	19980924 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Allen, Dyer, Doppelt, Milbrath & Gilchrist, P.A., 255 South Orange Avenue, Suite 1401, P.O. Box 3791, Orlando, FL, 32802-3791	
NUMBER OF CLAIMS:	15	
EXEMPLARY CLAIM:	1	
LINE COUNT:	380	

-cyclooxygenase 2 inhibitor

antiangiogenic combination for treatment of cancer)

ACCESSION NUMBER: 2002:192070 USPATFULL

TITLE: Antiangiogenic combination therapy for the  
treatment of cancer

INVENTOR(S): McKearn, John P., Wildwood, MO, UNITED STATES  
Gordon, Gary B., Highland Park, IL, UNITED STATES  
Cunningham, James, Chicago, IL, UNITED STATES  
Gately, Stephen T., Palatine, IL, UNITED STATES  
Koki, Alane T., Beaufort, MO, UNITED STATES  
Masferrer, Jaime L., Ballwin, MO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002103141	A1	20020801
APPLICATION INFO.:	US 2001-843132	A1	20010425 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1999-470951, filed on 22 Dec 1999, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-113786P	19981223 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Pharmacia Corporation, Corporate Patent Department, P.O. Box 5110, Chicago, IL, 60680-9889	
NUMBER OF CLAIMS:	181	
EXEMPLARY CLAIM:	1	
LINE COUNT:	8069	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

and/or an effective amount of indomethacin. Of these two, metronidazole is preferred. The present invention is further directed to methods of **treating** smooth muscle contraction, including the contraction of the uterus during, for instance, premature labor. The methods include administering a composition to a subject who has or is at risk of developing smooth muscle contractions a composition comprising an amount of a heterocycle-containing compound effective to prevent, or control by extending to substantially full-term, a premature labor. The heterocycle-containing compound present in the composition is a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof.

DETD [0076] The present invention is also directed to methods for modifying inflammatory responses that are mediated by PGE.sub.2. Prostaglandins, for instance PGE.sub.2, and leukotrienes (for instance LTB.sub.4), are known to arise during inflammation. In high levels, PGE.sub.2 is pro-inflammatory because it stimulates synthesis of IL-8, while in low levels, it can be cytoprotective, because of its capacity to stimulate cytokine IL-10 production. The latter cytokine (IL-10) downregulates inflammation, while the former (IL-8) signals the infiltration of polymorphonuclear neutrophils (a type of leukocyte) into the affected tissue. PGE.sub.2 is typically produced by a cell, for instance a damaged cell, is released by the cell and interacts with a receptor on a second cell. The second cell may be a leukocyte whose function is to release substances toxic for microorganisms. These substances include reactive oxygen species (including free hydroxyls, superoxide anion, and singlet oxygen), proteolytic enzymes, and acids. While toxic to microorganisms, they are also very toxic for the host's own tissues. It is expected that the prostaglandin analogs of the present invention, preferably PGE.sub.2-imidazole or PGE.sub.2-histidine, will bind to PGE.sub.2 receptors and inhibit the binding of PGE.sub.2, and possibly other prostaglandins. It is further expected that the binding of PGE.sub.2-imidazole or PGE.sub.2-histidine to a PGE.sub.2 receptor will not cause a response in the cell that includes the receptor. Examples of conditions that can be **treated** by modifying inflammatory responses that are mediated by PGE.sub.2 include, for instance, colibacillosis and mastitis in cattle, pancreatitis, Barrett's esophagus, gastroesophageal reflux disease syndrome (GERDS), and hepatitis.

DETD [0111] Considering that purified PGE.sub.2-imidazole inhibited cAMP formation in CT-stimulated CHO cells (FIG. 4), the capacity of this adduct to block CT-induced fluid accumulation in murine intestinal loops was tested. FIG. 5A shows that PGE.sub.2-imidazole, in doses as low as 100 .mu.g, instilled into the intestinal lumen significantly reduced CT-induced fluid accumulation. A dose of 200 .mu.g completely blocked fluid loss following CT challenge during the 6-hour observation period. The cAMP levels (FIG. 5B) in the intestinal loop fluids were markedly reduced by PGE.sub.2-imidazole **treatment** and coincided with the reduction in fluid accumulation.

DETD [0122] Mouse intestinal loops challenged with CT and dosed with L-histidine accumulated significantly less fluid than those from the corresponding CT-challenged control mice (FIG. 1). Generally, the observed dose of L-histidine, providing mouse intestinal loops with maximum protection against CT-induced fluid accumulation, was relatively large (592 mg/kg), even when **treatment** was initiated at the same time as toxin challenge (FIG. 1).

DETD [0124] L-histidine was demonstrated to react chemically with PGE.sub.2 (FIG. 3), and we considered the possibility that L-histidine inhibited the action of PGE.sub.2 in murine intestinal loops challenged with CT. It was demonstrated that the purified PGE.sub.2-imidazole adduct reduced cAMP levels in culture supernatants of CHO cells stimulated with CT (FIG. 4). It was surmised that L-histidine, as well as the PGE.sub.2-imidazole adduct, interfered with the activity of PGE.sub.2 in the CT-**treated** cells. It was not possible to measure the reduction of PGE.sub.2 in vivo or in vitro by PGE.sub.2-specific

radioimmunoassays, since the PGE.sub.2-histidine (or imidazole) adduct appeared to react equally well with antibodies to PGE.sub.2. In part, L-histidine could have served as a PGE.sub.2-inactivating compound, which provided additional support for the role of PGE.sub.2 in CT-induced secretion of water and electrolytes in the small intestine. Additionally, the PGE.sub.2-histidine covalent adduct could serve to inhibit the potential of PGE.sub.2 to stimulate adenylate cyclase. Indeed, purified PGE.sub.2-imidazole adduct inhibited CT-induced fluid accumulation in murine intestinal loops (FIG. 5A). In this case, the imidazole moiety may inactivate the native stimulatory effect of PGE.sub.2 on ion transport, but it is likely the structural similarity of the PGE.sub.2-adduct to PGE.sub.2 that enables it to interfere with the action of CT-induced PGE.sub.2 and fluid accumulation. Other PGE.sub.2 analogs (e.g., PGA.sub.2 and PGB.sub.2) also reduce CT-induced fluid accumulation in murine intestinal loops with lower potency.

DETD [0130] Adult female Swiss-Webster mice (25-30 g) were purchased from Taconic Farms, Inc. (Germantown, N.Y.) and housed in a specific pathogen-free animal facility at UTMB in Galveston, Tex. Mice were fasted for 18 hr before surgery to reduce the food content of the small intestine. A ventral midline incision was made under ether anesthesia to expose the small intestine. A single 5-cm segment of small intestine, ligated with "00" silk suture, was injected with 1 .mu.g of cholera toxin (CT) in 100 .mu.l. After 6 hours observation, the animals were euthanized by cervical dislocation and the intestinal loops were removed. The amount of luminal fluid was measured and expressed as .mu.l/cm, while the tissue was prepared for light or electron microscopy. In some experiments, intestinal challenge was accomplished by injecting 100 .mu.g of CT followed immediately with 160 .mu.g/100 .mu.l **celecoxib** (dissolved in 3% dimethylsulfoxide in phosphate buffered saline) at the time of challenge. Fluid volume was measured 6 hours after challenge. Specimens of fluid and tissue were collected at time of necropsy.

DETD [0131] The inhibitory effect on CT-induced fluid accumulation was observed with dosages of **celecoxib** reported to be specific for COX-2.

DETD [0133] FIG. 11 shows that CT-induced fluid accumulation in murine intestinal loops is significantly reduced by **celecoxib**.

DETD [0142] The results indicate that **celecoxib**, PGE.sub.2-histidine, and imidazole each inhibit adenylate cyclase enzyme activity (FIG. 12). The data in FIG. 12 also show the absence of adenylate cyclase inhibition by SC560 and **rofecoxib** under the conditions tested. FIG. 13 shows that SC560 inhibits cholera toxin-induced fluid secretion, although it has not been demonstrated that it does so by inhibiting adenylate cyclase under the conditions tested (FIG. 12). **Rofecoxib** does not inhibit cholera toxin-induced secretion under the conditions tested. **Celecoxib** was designed to be a highly specific inhibitor of cyclooxygenase-2 (COX-2). The mechanism by which **celecoxib** inhibits adenylate cyclase is not known; however, it was observed that imidazole also inhibits adenylate cyclase. Since imidazole is part of the chemical structure of **celecoxib**, it is suspected that this moiety participates in the functional activity of inhibiting adenylate cyclase. Imidazole is known to bind divalent cations (e.g., Mg.sup.++, Zn.sup.++, and Ca.sup.++), and these metal cations are known to be required for adenylate cyclase activity. In fact, a recent report in which the X-ray crystallography-derived structure of rat adenylate cyclase was determined showed that there were two binding domains in the catalytic site of adenylate cyclase divalent cations (Zn.sup.++ and Mg.sup.++). We suspect that the imidazole group of **celecoxib** is enabling the drug to bind to the metal ions in the enzyme's active site, which would block the substrate (ATP) from entering. The end result would be inhibition of adenylate cyclase activity. From a physiological perspective in the small intestine, such an inhibitor would reduce or block cholera toxin-induced fluid loss (**diarrhea**).

DETD [0145] The adenylate cyclase enzyme assay was performed as described earlier in Example 1; however, the assay was used to assay various inhibitors (e.g., PGE.sub.2-histidine, **celecoxib**, and imidazole). The amount of enzyme in each experiment was 0.46 nmole, and the concentration of each inhibitor was varied in order to determine the dose that would block 50% of the enzyme activity (IC.sub.50).

DETD [0147] The results summarized in the FIGS. 14-16 indicate that adenylate cyclase can be inhibited, which forms a strategy for reducing or blocking intestinal fluid secretion induced by several agents of diarrheal disease. FIG. 14 shows the dose response for PGE.sub.2-histidine in inhibiting adenylate cyclase. The IC.sub.50 dose of PGE.sub.2-histidine inhibiting 50% of the enzyme activity (0.46 nmole) was 21.5 .mu.mole. FIG. 15 shows that when a similar experiment was performed with **celecoxib**, and its IC.sub.50 dose was 20 mmole. FIG. 16 shows that imidazole alone exhibited inhibited adenylate cyclase activity; however, it was less potent (IC.sub.50=1.57 mmole). Table 1 summarizes the inhibitory potencies of the various adenylate cyclase inhibitors. Similar results were observed when edema factor from B. acthracis was used as the adenylate cyclase.

TABLE 1

Molar concentration of commonly available drugs required to inhibit Adenylate Cyclase

Enzyme:Drug	Ratio
Adenylate Cyclase: <b>Celecoxib</b>	0.46 nm:20.0 .mu.m
Adenylate Cyclase:Imidazole	0.46 nm:1.57 mm
Adenylate Cyclase:Histidine:PGE.sub.2	0.46 nm:21.5 .mu.m

Adduct

CLM What is claimed is:

8. The method of claim 6 wherein the diphenyl heterocycle derivative is **celebrex** or DuP-697.

16. The method of claim 15 wherein the diphenyl heterocycle derivative is **celebrex** or DuP-697.

24. A method for **treating** intestinal fluid loss in a subject, the method comprising administering to a subject who has or is at risk of developing intestinal fluid loss a composition comprising an effective amount of a heterocycle derivative selected from the group consisting of a diphenyl heterocycle derivative, a prostaglandin analog, and a combination thereof, wherein the fluid loss is not associated with a pathogen polypeptide having ADP-ribosylation activity.

35. A method for **treating** intestinal fluid loss in a subject, the method comprising administering to a subject who has or is at risk of developing intestinal fluid loss a composition comprising an effective amount of a heterocycle-containing compound, wherein the intestinal fluid loss is associated with a pathogen polypeptide having ADP-ribosylation activity.

43. The method of claim 35 wherein the heterocycle derivative is not **celecoxib**.

47. A method for **treating** whooping cough in a subject, the method comprising administering to a subject who has or is at risk of developing whooping cough a composition comprising an effective amount of an heterocycle-containing compound.

55. A method for **treating** anthrax in a subject, the method comprising administering to a subject who has or is at risk of developing anthrax a composition comprising an effective amount of a heterocycle-containing compound.

IT 53-86-1, Indomethacin 71-00-1, L-Histidine, biological studies  
288-32-4, Imidazole, biological studies 443-48-1, Metronidazole  
88149-94-4 162011-90-7 169590-42-5 188817-13-2  
(heterocycle derivs. for inhibiting adenylate cyclase and methods of  
use for treating intestinal fluid loss and whooping cough and anthrax  
and conditions assocd. with smooth muscle contraction)

ACCESSION NUMBER: 2002:55065 USPATFULL  
TITLE: Heterocycle derivatives and methods of use  
INVENTOR(S): Peterson, Johnny W., Dickinson, TX, UNITED STATES  
Gessell-Lee, Deborah L., Galveston, TX, UNITED STATES  
Saini, Shamsher S., Dickinson, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002032228	A1	20020314
	US 2002188016	A9	20021212
APPLICATION INFO.:	US 2001-860652	A1	20010519 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-210412P	20000608 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	MUETING, RAASCH & GEBHARDT, P.A., P.O. BOX 581415, MINNEAPOLIS, MN, 55458	
NUMBER OF CLAIMS:	62	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	20 Drawing Page(s)	
LINE COUNT:	1668	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L200 ANSWER 6 OF 36 USPATFULL

TI Crohn's disease diagnostic and **treatment** methods and compositions

AB A composition and method for detecting Crohn's disease include the use of serological testing as a rapid and simple way to diagnose Crohn's disease. The serological tests were based on the use of the two recombinant clones isolated from an M. paratuberculosis genomic library that expressed 35K and 36K MW antigens. Antigen p35 was isolated from Johne's disease sera (acid-fast bacilli form) and p36, from human CD sera (spheroplast form). The combined use of p35 and p36 recombinant antigens provides a highly specific and sensitive test to demonstrate the humoral immune response of CD patients to M. paratuberculosis. A serologic kit is disclosed including the composition including the combined p35 and p36 antigens. A **treatment** methodology utilizes antimycobacterial drugs, preferably upon patients prescreened for the presence of M para. A particular antibiotic regimen includes an administration of both rifabutin and clarithromycin, which has been found to be particularly effective in alleviating the symptoms of Crohn's disease.

SUMM The present invention relates to compositions and methods for diagnosing and **treating** Crohn's disease, and, more particularly, to such compositions and methods for screening for a presence of a bacterium believed involved in causing Crohn's disease and for **treating** patients shown by the screening method to be infected with the bacterium.

SUMM Common symptoms of Crohn's disease include abdominal pain and **diarrhea**. There may also be **rectal bleeding**, weight loss, and fever. The bleeding may be serious and persistent, leading to anemia. Children may suffer delayed development and stunted growth.